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AUGUST, 1918

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American Journal of Diseases of Children

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NEUROBLASTOMA SYMPATHICUM

REPORT OF A CASE, WITH NOTES ON TWO OTHERS, AND A BRIEF REVIEW OF THE LITERATURE *

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AND
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CASE 1.—Charles C., 4 years and 3 months old, was admitted to the Children's Hospital, Dec. 31, 1917. His family history was good. He was born at full term, and had always been well, except for rather frequent "colds" during his infancy. His mother thought that his abdomen had always been large, but she had not noticed it especially until two weeks before, since when it had increased in size very rapidly. He began to fail rapidly about the same time and the last week had been confined to bed. Since being in bed he had been somewhat short of breath and had had an unproductive cough. His appetite was fair, he did not vomit and his bowels were regular. He had no symptoms pointing to trouble in the urinary tract.

Physical Examination.—He was pale and poorly developed, and showed some evidences of old rickets. His tongue was slightly coated. The throat, heart and lungs were normal. The abdomen was markedly distended and the superficial veins slightly enlarged. The lower border of the liver was palpable, hard and sharp, 6 cm. below the costal border in the right nipple line, 8 cm. below the ensiform and running under the left costal border in the anterior axillary line. The surface was smooth, hard and slightly tender. The spleen was not made out. The kidneys were not palpable and there was no unusual resistance in the flanks. There were no evidences of free fluid in the abdomen. The genitals were normal and the rectal examination was negative. There was slight edema of the legs. There were no evidences of any involvement of the nervous system.

The urine was acid and cloudy from urates, but contained no albumin or sugar. The sediment was negative.

The blood showed: hemoglobin, 60 per cent. (Sahli); red corpuscles, 2,000,000; white corpuscles, 5,500; mononuclears, 40 per cent.; transitionals, 4 per cent., and polynuclear neutrophils, 56 per cent.

The red corpuscles showed slight achromia, but no variation in size or shape.

The tuberculin test was negative to both the human and bovine types.

The Wassermann test was negative.

The liver increased very rapidly in size, and edema of the scrotum, back and legs became marked. He lost very rapidly in weight and strength and

* Submitted for publication June 3, 1918.
* From the Children's Hospital.
* Read at the Annual Meeting of the American Pediatric Society, Lenox, Mass., May, 1918.

died Jan. 6, 1918, one week after his admission and three weeks after the symptoms were first noted.

The diagnosis during life was sarcoma of the liver, which, in spite of the rarity of the condition, was thought to be primary rather than secondary, because no primary focus of disease could be found elsewhere.

Necropsy.—A restricted necropsy was performed by Dr. S. B. Wolbach, fifteen and a half hours after death. The head was not opened. The throat, heart, lungs, gastro-intestinal tract, pancreas and pelvic organs showed nothing abnormal. The peritoneal surfaces were smooth and glistening. The mesenteric lymph nodes were not enlarged.

Liver: The lower border of the liver extended down to the crest of the right ilium and in the median line was 14 cm. from the ensiform. The enlargement of the liver was almost symmetrical. The suspensory ligament was pushed over to the left owing to the great enlargement of the right half of

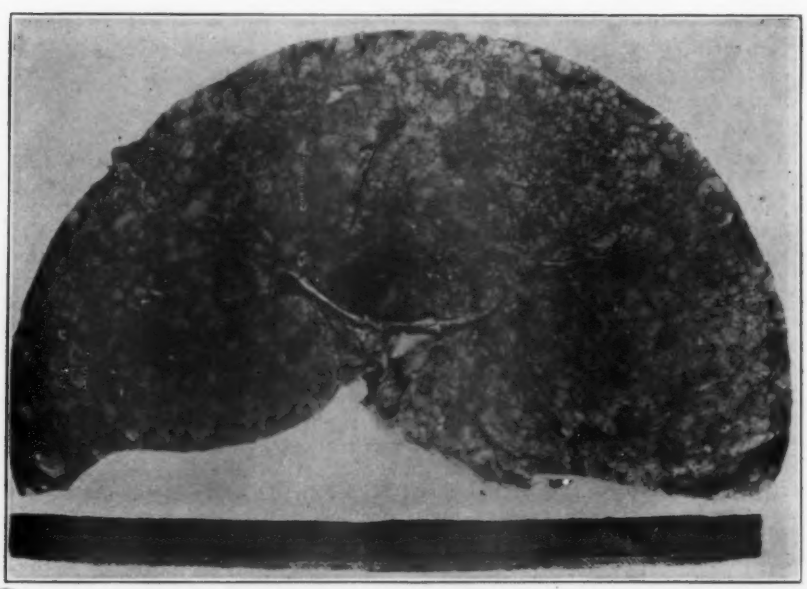


Fig. 1.—Photograph of a section of a Kaiserling specimen of the liver, Case 1. The scale is in inches.

the liver and the anterior border of the right lobe was deeply notched a few centimeters to the right of the median line of the body. The liver weighed 2,050 gm. The capsule was smooth. The color was pale red and reddish yellow, mottled with fatty, opaque areas which were not elevated above the surface. These areas varied in size from 1 mm. to 1 cm. in diameter. The liver was extremely friable. Section showed surfaces bearing very little resemblance to normal liver tissue (Fig. 1). As a whole, the cut surfaces had a translucent appearance. There were distinct areas of translucent white tissue, circular in shape, all produced by the confluence of circular areas, thickly distributed throughout the whole of the liver. There were other large areas 4 to 15 mm. in diameter which were soft, deep red and bulging slightly from the cut surfaces. Here and there were narrow bands and small areas of brownish liver tissue, but everywhere paler than normal. It was quite evident that the whole of the liver was infiltrated with a soft new growth.

The gallbladder and bile passages were patent and normal. Accompanying the cystic duct was a lymph node, 8 by 4 mm., which was soft, translucent white.

Spleen: The spleen was enlarged and measured 10 by 6 cm. The capsule was smooth; the color, salmon red. On section the cut surfaces were everywhere smooth and normal in appearance, except for a slightly paler color than is normal. The splenic corpuscles were visible and appeared normal.

Kidneys and Adrenal Glands: The kidneys were normal in size, color, markings and consistency. Partly overlying the left kidney and extending to the median line was a tumor mass (Fig. 2). The kidney itself was not connected with this tumor growth. Section of the tumor mass revealed its intimate relation with the adrenal gland. The tumor mass, as a whole, including the adrenal gland, was 8 cm. in length and 4 to 5 cm. in width. The superior end of the adrenal gland was recognizable. There was a triangular piece of adrenal present which measured 2.5 by 2.5 cm. Extending downward behind the tumor mass was a band of adrenal cortex, 4 cm. in length and from 6 to 8 mm. in width. This arm of the adrenal was not adherent to the tumor

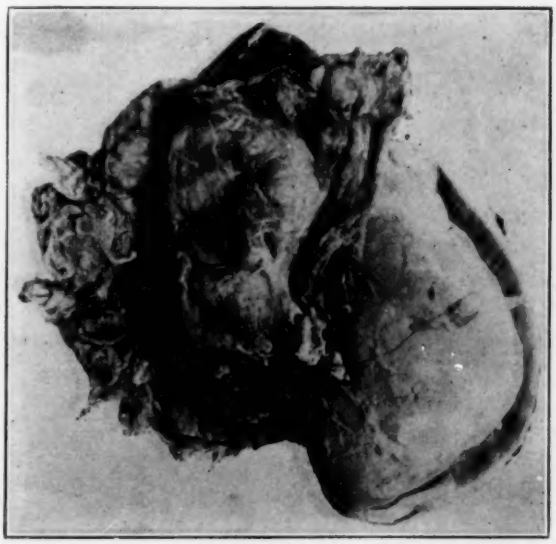


Fig. 2.—Photograph of the primary tumor of the adrenal and the kidney, Case 1.

mass as a whole. In the center of the triangular portion of the adrenal gland first mentioned, was an elevated, white tumor nodule 8 mm. in diameter. Beneath this there bulged from the substance of the adrenal a tumor mass, 5 cm. in length, composed of three nodules, the superior one, 1 cm. in diameter, the middle one 3 cm., the inferior 2 cm. A section through the adrenal showed that the first mentioned tumor nodule extended into the substance of the adrenal and a cut section showed irregular borders. The color was grayish white. Beneath that there was a nodule, 1 cm. in diameter, soft and dark red. Section of the largest nodule, which was 3 cm. in length, presented in part firm white friable tissue, in part dark red necrotic material with many small gritty areas. The inferior nodule composing the main tumor mass was dark red, soft, and apparently composed of necrotic tumor tissue. There were numerous large lymph nodes lying between this tumor mass and the median line and grouped around the celiac exis. These lymph nodes varied in size

from 3 to 8 mm. On section they were soft, translucent and white. The right adrenal gland was normal.

Frozen Section of Tumor: Frozen sections of the tumor, after hardening in formaldehyd solution, showed in the liver almost complete replacement of the liver parenchyma by small round cells with deeply stained nuclei. In some places the destruction of the liver tissue was complete, in others the liver columns could be recognized much flattened and distorted.

Sections of the tumor of the adrenal showed a small round cell tumor with a delicate reticular framework. Portions of this tumor were necrotic and portions were fibrous, but other portions showed a rosette grouping of the cells surrounding a central granular or fibrillar mass, characteristic of ganglioma embryonale sympathicum or neuroblastoma sympathicum.

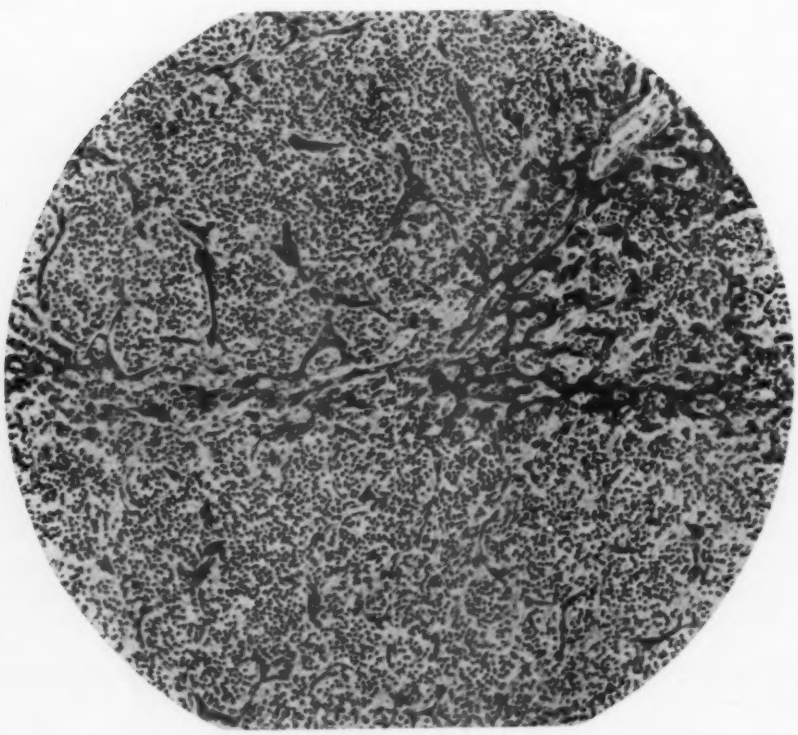
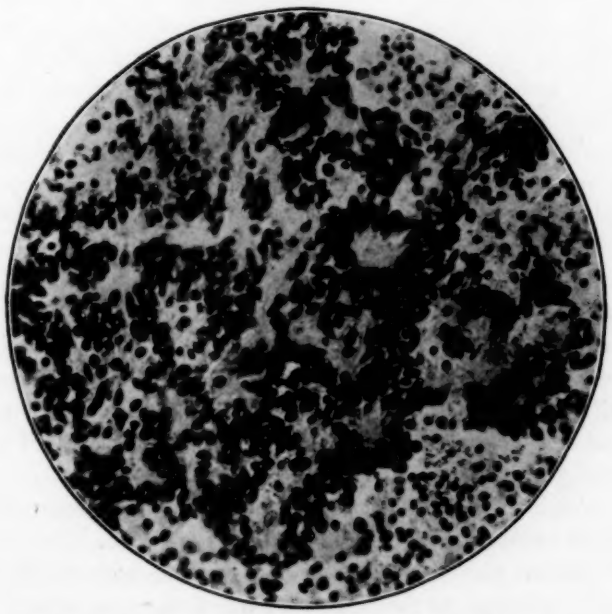


Fig. 3.—Low power photomicrograph of a section of the liver, Case 1; about 125 diameters.

Microscopic Examination.—The tissues were fixed in Zeuber's fluid and stained with eosin-methylene blue.

Liver: There is very little liver tissue remaining. The organ was largely replaced by a new growth consisting of exceedingly minute cells, smaller than lymphoid cells, most of them with densely staining homogeneous nuclei, having the appearance of pyknotic or postmortem nuclei. This appearance of the nuclei is probably due to richness in chromatin, as the preservation of other cells, that is, liver cells and bile ducts, is perfect (Fig. 3). The liver tissue is present in the form of anastomosing strands, in which the liver cells are usually much distorted, but occasionally they are almost normal in appear-

ance. The intervening tissue filled with the tumor is traversed with delicate epithelial tubules, which probably represent regenerated bile ducts. In other places, where the tumor is actively invading, there are all degrees of atrophy and degeneration of the liver cells, and it is possible to see that the tumor cells are growing between the liver columns and endothelium of the sinusoids, although in most places such details of structure are entirely obliterated. The tumor cells are small, the cytoplasm is extremely scanty in amount and difficult to demonstrate. There are occasional clusters of slightly larger cells with nuclei less densely stained and containing scattered particles of chromatin. The cells, however, are embedded in a finely granular material, which in places can be seen to have a linear striated effect suggestive of protoplasmic fibrils. In some portions of the liver the replacement by tumor cells is so complete as to obliterate all trace of liver. There are many mitotic figures among the tumor cells.



4. Photomicrograph of the primary tumor of the adrenal gland, Case 1; about 400 diameters.

Adrenal Gland: Sections through the adrenal gland containing the primary tumor showed the bulk of the tissue to be composed of minute cells similar to those in the liver metastasis. There are places, however, where there is a very perfect "rosette" formation, consisting of larger cylindrical and pyriform cells arranged about a central mass of granular material (Fig. 4). This central granular material can be resolved in places into very delicate fibrils and the latter in some instances can be traced into the pyriform tumor cells. The stroma consists of a delicate vascular fibrous tissue. The tumor is a rapidly growing neuroblastoma, of sympathetic ganglion cell origin.

Lymph Node: Sections of a lymph node adjacent to the tumor mass showed complete replacement by the exceedingly minute type of tumor cells.

Celiac Ganglia: These are almost completely replaced by the tumor cells, which are always of the very small type.

Spleen: The malpighian bodies are of normal size and shape. A few contain hyaline masses and reticular hyaline material. The pulp contains many eosinophils of the myeloid type. The venules contain groups of cells which are possibly tumor cells, since many of them were smaller than lymphocytes and have deeply stained nuclei.

Kidneys and Right Adrenal Gland: These were normal.

DISCUSSION

From the liver alone the diagnosis of neuroblastoma would have been impossible to prove, although warrantable, as numerous instances are recalled in which the cells in the metastases from neuroblastomata primary in the adrenals have had the appearances characteristic of this case. The diagnosis in this case is established by the presence of the tumor in the adrenal showing a greater degree of differentiation of the cells evidenced by the formation of protoplasmic fibrils and the arrangement into ball masses which in section produce the rosette appearance.

The essential element in the tumor for diagnosis is the fibrils. The fibrils are not to be compared with the coarser, more or less specifically staining fibrils associated with connective tissue and neurogalia cells. They are in reality delicate protoplasmic processes and are representative of axis cylinder processes. There is no special stain for their demonstration.

The earliest diagnosis based on the presence of these fibrils in malignant tumors of the adrenal gland was that of glioma. Virchow[1] and Marchand[2], in 1891, recognized the nervous character of a tumor of the adrenal and compared the cells with the neuroblasts of the fetal sympathetic ganglia.

J. H. Wright[3], in 1910, focused attention to this group of tumors and collected twelve cases, including four of his own. He briefly and succinctly showed that the tumor cells associated with the fibrils have the "same morphology as the cells from which the sympathetic nervous system and the medulla of the adrenal develop and which are regarded by embryologists as arising from migrated primitive nerve cells." Wright offered the names neurocystoma and neuroblastoma as equally applicable.

Pick and Bielschowsky[4], in 1911, in a classification of tumors of nerve tissue origin, gave the name ganglioma embryonale sympathicum to the tumors described by Wright. Pick[5], in 1912, collected a total

1. Virchow: Die Krankhaften Geschwulste, Berlin, 1863-1865.
2. Marchand: Festschr. f. R. Virchow; Internat. Beitr. z. wissensch. Med., Berlin, 1891, 578.
3. Wright, J. H.: Jour. Exper. Med., **12,** 556.
4. Pick and Bielschowsky: Ztschr. f. d. ges. Neurol. u. Psychiat., **6,** 391.
5. Pick: Berl. klin Wchnschr., **49,** 16.

of eighteen cases, including one of his own, and discussed fully and adequately the origin and the relationship of the tumors arising from the primitive nerve cells. These tumors may represent any of the potentialities of the primitive cells, which are nerve cells, glia cells and chromaffin cells. The tumors representing nerve cells with which we are now dealing may be either rapidly growing and undifferentiated or more slowly growing and more highly differentiated into ganglion cells. He completely substantiated Wright's conclusions.

Landau,[6] independently of Pick, in the same year, published a similar classification and discussion of these tumors. He added three cases of his own and uses the name malignant sympathetic neuroblastoma. From this time on the origin and classification of these tumors has been accepted and numerous new cases have been added.

The paper of Herxheimer,[7] in 1913, covers substantially the same ground as those of Pick and Landau. He chooses Landau's name, neuroblastoma sympathicum, in preference to Pick's ganglioma embryonale sympathicum, a choice which has proved to be in accordance with the preference of subsequent writers.

Two American papers, each introducing a new case, by Wahl[8] and Lehman,[9] are comprehensive and adequate to orient any one desiring more information on the subject of neuroblastoma. Lehman has collected a total of twenty-five cases of sympathetic neuroblastomas and several doubtful cases.

Hertz and Sacher's[10] case is the most recent one recorded and in the rapid growth of the liver metastasis bears some resemblance to our case.

Our case is noteworthy for the rapidity of the growth of the liver metastases, which overshadowed all other signs, and the absence of apparent metastases elsewhere. As a complete necropsy was not permitted, early metastases to the bones can not be excluded. It is our opinion that these tumors are not as rare as the small number of published cases would indicate and for this reason we append the reports of two other cases from the surgical service of the Boston Children's Hospital.

CASE 2.—W. D. MacN., aged 7 months, was admitted June 12, 1917. His past history and family history are irrelevant. May 4 a physician noticed a mass in the right side of the abdomen which was not tender and which did not noticeably increase in size. The physical examination showed a well nourished infant. The skin, eyes, ears, nose, mouth and throat were all

6. Landau: Frankfurter Ztschr. f. Path., **11,** 26.
7. Herxheimer: Beitr. z. path. Anat. u. Path., **57,** 112.
8. Wahl: Jour. Med. Research, **30,** 205.
9. Lehman: Jour. Med. Research, **36,** 309.
10. Hertz and Secher: Hospitalstidende, **60,** No. 45; abst. Jour. Am. Med. Assn., 1918, **70,** 278.

negative. The heart and lungs were normal. The reflexes were normal. The abdomen showed a bulging in the right upper quadrant. Palpation showed a hard irregularly shaped mass occupying the whole of the upper and a third of the lower right quadrant. It was not tender. It descended with respiration, was not attached to the abdominal wall and by rectal examination the lower end was found to be freely movable.

An exploratory operation was done on June 14. The tumor was found to be inoperable and a small piece was removed for microscopic examination. The abdomen contained a slight excess of fluid in the flanks. The tumor was hard, nodular and not cystic and extended from the right costovertebral angle to below the brim of the pelvis and inward beyond the median line. It overlay the aorta and vena cava. The ascending colon was displaced forward and inward and crossed vertically the median aspect of the tumor.

Death occurred seven hours after the operation. Permission for a necropsy was refused.

The material was fixed in Zenker's fluid and stained with eosin-methylene blue, Mallory's phosphotungstic acid hematoxylin, Van Gieson's stain and hematoxylin and eosin. The photomicrographs were made from sections stained with hematoxylin and eosin.

Microscopic Examination.—The tumor is composed mainly of small round cells irregularly arranged in masses which are separated by a delicate fibrous tissue stroma giving an alveolar appearance. The tumor cells vary in size and the nuclei contain a variable but large amount of chromatin. The cytoplasm is small in amount and usually difficult to demonstrate. There are groups of larger elongated cells in compact masses but there is no rosette grouping in the sections. Delicate fibrils are very numerous throughout the tumor between individual cells and in large masses of parallelly arranged wavy fibrils lying between the groups of tumor cells and stroma or extending between adjacent clumps of tumor cells. There are many mitotic figures and a rare type of larger cell with abundant cytoplasm suggesting a ganglion cell. The tumor is a typical malignant neuroblastoma sympathicum identical with many of the reported cases (Figs. 5 and 6).

CASE 3.—Myrtle P., aged 2 years and 2 months, was admitted to the outpatient department, March 2, 1918, for swelling and tenderness at the left knee, attributed to a fall one week previously. The knee was swollen, not red, slightly tender. There was limitation of motion to 20 degrees extension and 60 degrees flexion. A roentgenogram made March 5 shows widening of the lower end of the diaphysis of the femur with areas of rarefication just above the epiphyseal line. A mass was noticed in the abdomen and the child was admitted to the hospital March 9.

Her past history and family history are irrelevant. The child was well nourished and well developed. The cranium, eyes, ears, nose, teeth, mouth and throat were negative. The heart and lungs were normal. The reflexes and skin were normal. The extremities with the exception of the left knee were normal. The abdomen was rounded and tympanitic, with the exception of the left upper and middle quadrants. In the left upper quadrant there was felt a hard rounded mass which did not move when the position of the child was shifted. It was smooth, not tender.

An operation, March 11, showed a large tumor of the left kidney. This was enucleated and found to be adherent posteriorly. It extended upward to the diaphragm, where there was a cyst. The cyst ruptured and a considerable quantity of brown semisolid material escaped. After removal of the tumor there was but little bleeding from the cavity, but inspection showed that there were nodules of the growth extending downward along the vertebral column and out into the broad ligament on the left side.

Death occurred March 28, presumably hastened by a low grade infection of the peritoneum.

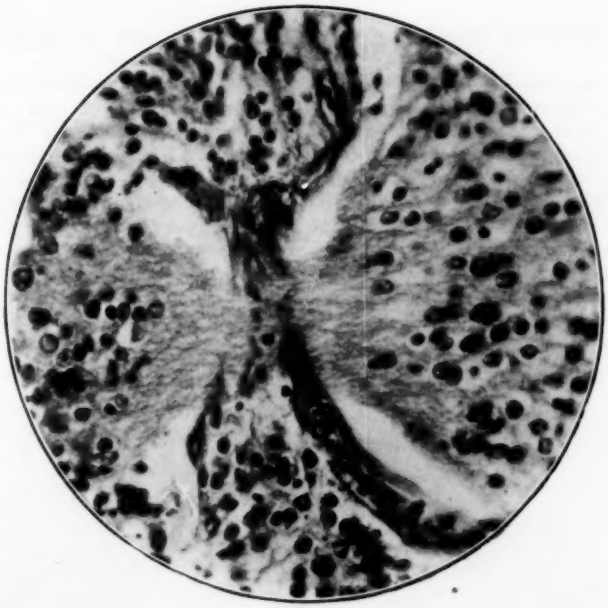


Figure 5

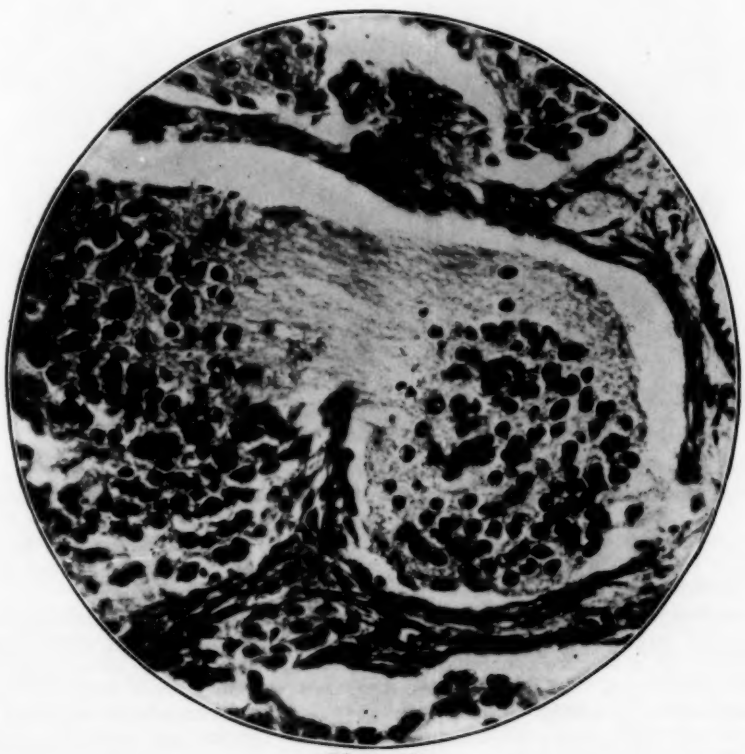


Figure 6

Figs. 5 and 6.—Photomicrographs from Case 2, showing masses of fibrils extending between clumps of tumor cells; about 400 diameters.

Pathologic Report.—The specimen consisted of a kidney partly replaced by tumor. It was moderately firm and measured 13 by 7 by 5 cm. The lower pole was evenly rounded. At the upper pole there was a loss of substance involving the pelvic border of the kidney, about 3.5 cm. in diameter. There was in this location an irregularly circular yellow and red mottled crater, the base of which was formed of granular friable material. At the periphery of this crater there was attached a grayish membrane continuous with the capsule of the kidney and which probably was the remains of the capsule overlying the necrotic mass. A section through this pole of the kidney showed an irregular zone of yellowish red mottled tissue, 1 to 2 cm. deep, and inferior to this the kidney substance appeared to be normal.

Microscopic Examination.—The tissue was fixed in Zenker's fluid and 10 per cent. formaldehyd. The description is based on sections stained with eosin-

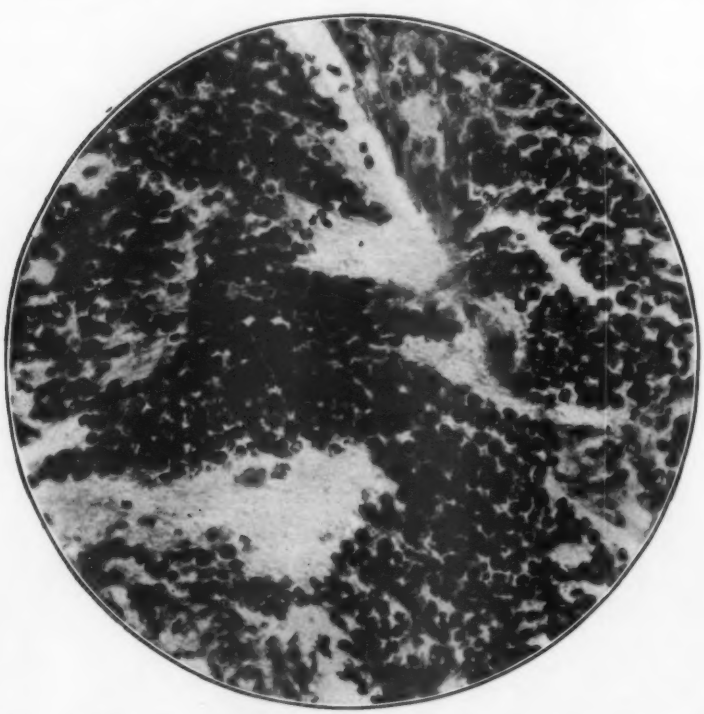


Fig. 7.—Photomicrograph, Case 3, showing bundles of fibrils between masses of the tumor cells and between the tumor and the stroma; about 400 diameters.

methylene blue, Van Gieson's stain and Mallory's phosphotungstic acid hematoxylin stain. The photomicrographs were made from sections stained with hematoxylin and eosin.

Sections through the upper pole of the kidney show a new growth consisting of large anastomosing columns of tumor cells with many mitoses and supported by a delicate connective tissue stroma. Most of the tumor cells are small and round. In many places there are elongated oval and pyriform-shaped cells. The latter have a finely granular cytoplasm which can often be traced out into long delicate processes. The nuclei are relatively large, vesicular in type and contain a large amount of chromatin in the form of a coarse network (Fig. 8). The amount of cytoplasm is very scanty and as a

rule is eccentrically situated in relation to the nucleus. The size of the cells is slightly larger than the size of lymphocytes found in the germinal centers of lymphoid follicles. Here and there throughout the tumor there are very delicate fibrils occurring in small bundles between the tumor cells and extending between adjacent clumps of tumor cells (Fig. 7). These fibrils are also found in bundles of considerable size lying between the connective tissue stroma and the tumor cells. The fibrils are exceedingly delicate and have a granular structure and bear no resemblance to the deeply staining intercellular fibrils of connective tissue and neuroglia (Fig. 8). There is no rosette formation but the diagnosis of neuroblastoma sympathicum is established beyond question by the presence of the delicate nerve fibrils.

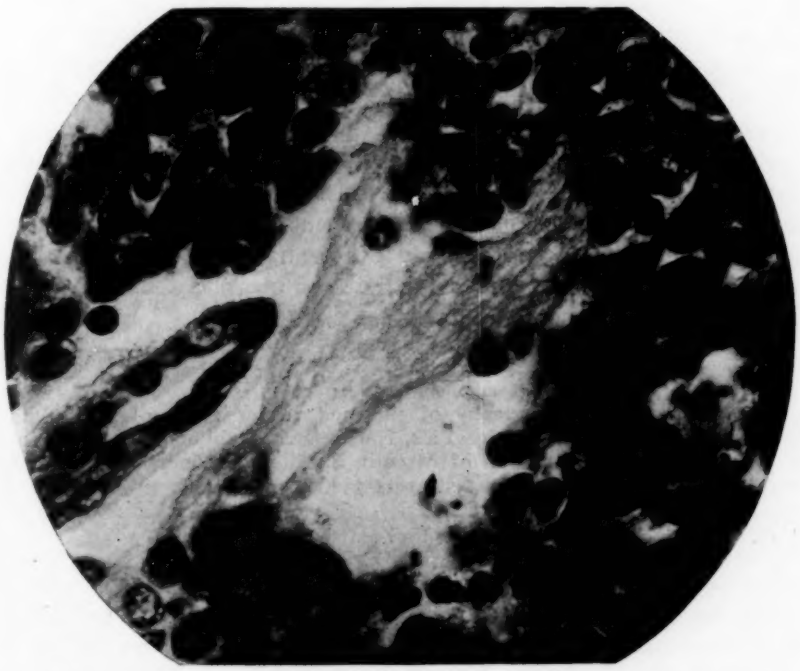


Fig. 8.—Higher power photomicrograph of a section from Case 3, showing the character of the nuclei and the fibrils; about 800 diameters.

No postmortem was obtained and therefore the location of the primary tumor cannot be proved. The extensive loss of substance and invasion of the kidney at the upper pole indicate, however, that the tumor took origin from the adrenal gland.

These three cases present the slight differences in the histology exhibited by this type of tumor. In the first case we have rosette formation in the primary tumor and in the metastases extreme rapidity of growth without rosette formation or fibril formation. The density of the nuclei is indicative of a large chromatin content and rapidity of growth, as has been noted by other authors. In the second and third cases no rosette formation was found. Fibril formation was abundant

in the second case, less abundant in the third, which represents a type easily overlooked. These three cases bring the number of undoubted cases of neuroblastoma sympathicum to twenty-nine, of which twenty were primary in the adrenal gland. The others have taken origin in sympathetic ganglia (three), retroperitoneal tissues (three), coccygeal gland, nose and uterus. It is highly probable that many other cases of primary tumors of the adrenal gland reported as sarcomas were neuroblastomas, as, for instance, the fourteen cases of adrenal tumors with cranial metastases collected by Tileston and Wolbach.[11] Of all the cases reported, but one patient survived, Lehman's case,[9] the only successful operative removal of a tumor of this type in an infant.

Since a variety of terms have been used to designate the malignant tumors representing a primitive type of sympathetic ganglion cells, it seems advisable to indicate a choice. Wright's terms neurocytoma and neuroblastoma are too inclusive. Ganglioma embryonale sympathicum, introduced by Pick and Bielschowsky, has been regarded by several authors as unsatisfactory because of the employment of ganglioma by others to designate a more highly differentiated type of nerve cell tumor. Our own preference is for the term neuroblastoma sympathicum or sympathetic neuroblastoma.

REFERENCES

For the complete bibliography of this and related types of tumors the articles of Pick and Bielschowsky, Pick, Herxheimer, Wahl and Lehman should be consulted. The presentation of cases in the literature in tabular form by Wahl and by Lehman makes their papers particularly useful.

11. Tileston and Wolbach: Am. Jour. Med. Sc., June, 1908.

VARIATIONS IN THE LIPOID ("FAT") CONTENT OF THE BLOOD OF INFANTS UNDER CERTAIN NUTRITIONAL CONDITIONS*

W. McKIM MARRIOTT, M.D. AND WARREN R. SISSON, M.D.
ST. LOUIS BOSTON

Clinical experience has shown that without a certain amount of fat in the food of an infant, normal growth is not be be expected. Excessively high fat feeding, on the other hand, may overtax the assimilative functions of the body and lead to most serious consequences. Thus intestinal indigestion with diarrhea and a lowering of the tolerance for all food is, at times, the result of an excessive amount of fat. Failure to gain weight, constipation, the conditions variously described as "Chronic Fat Indigestion," "Milchnährschaden," "Bilanzstörung," have all been attributed to relative or absolute excess of fat in the diet.

The infant fed on considerable amounts of fat, but unable to utilize this fat, is virtually in a state of fat starvation. Analyses of the stools for fat or its derivatives gives us some information as to the efficiency with which fat of the food is digested and absorbed. Further information as to the behavior of fat in the body of the infant can be obtained from a study of the fat of the circulating blood under varying conditions of feeding and states of nutrition.

If the fat of the blood represented only absorbed food fat on the way to the tissues, blood fat determinations would give us a reliable index of the amount of fat digested and absorbed. The process is not so simple, however, on account of the fact that the fat of the blood is derived from the tissues as well as from the food and there is no method at present available that will serve to differentiate the source of the fat. It has been shown that animals during complete and prolonged starvation may have as high a fat content of the blood as those fed on diets containing moderate amounts of fat.[1]

The reason for this is made clear when we consider the physiology of fat metabolism. Fat is absorbed largely by the mesenteric lymphatics and reaches the blood stream by way of the thoracic duct. There is reason for believing that this fat must be altered in some way; for example, the change from single to double bond linkages at places in

* Submitted for publication May 29, 1918.
* From the Boston Floating Hospital.
* Read at the Annual Meeting of the American Pediatric Society, Lenox, Mass., May, 1918.

1. Bloor, W. R.: Jour. Biol. Chem., 1914, **19**, 1.

the fatty acid molecule,[2] before it can be "burned" in the body. The view at present most generally accepted is that these preparatory changes take place in the liver, and that whatever part of the ingested fat is immediately needed for fuel requirements is intercepted by the liver and converted into the combustible form. The remainder is transported by the blood to the fat depots of the body, in the subcutaneous tissues and elsewhere, and there deposited. These deposits may be drawn on from time to time as the body may require, and the fat transported by the blood stream back to the liver and subsequently burned.

It is thus evident why, during starvation, when the fat depots are drawn on, there may be considerable amounts of fat in the blood stream. If, however, fat is being burned in an efficient manner the amount in the blood stream would not be expected to rise to an excessively high point, and this, indeed, corresponds to the observed facts. As some fat is always being burned there is always fat in the blood, coming either from the intestine or from the fat depots. In normal adults the amount of fat does not vary greatly except following the feeding of considerable fat. If the fat were absorbed from the intestine at the same rate at which it was utilized in the body the blood fat percentage should not change very much. If fat absorption were more rapid than utilization, a high blood fat would result and the excess would be deposited in the fat depots.

A similar condition occurs when fat is drawn from the fat depots more rapidly than it can be utilized. This happens under certain pathologic conditions and the excess fat is deposited in the liver. In general, high fat in the blood means a deposition of fat somewhere in the body.

In order to interpret the analyses of blood for fat it is necessary to know the diet of the patient. An infant fed reasonable amounts of carbohydrate and protein would not be starving; consequently the fat depots would not be called on to as great an extent as during starvation. As a result, blood fat would not be as high as during complete starvation. If a certain amount of fat were added to the diet and none were absorbed, blood fat would remain low. With absorption, however, blood fat would be expected to rise. Hence, of two infants on the same feedings, the one digesting and absorbing fat would be expected to show the higher blood fat. Further, the one with the higher blood fat should be depositing fat in the subcutaneous tissues and other fat depots and therefore gaining weight. We have endeavored to determine if this is actually the case; that is, whether infants gaining weight have higher blood fat percentages than those who are stationary or losing in weight.

2. Leathes: The Fats, London, 1913.

The nutritional condition of an infant may be considered from two standpoints, the first of which has just been mentioned, and may be referred to as the nutritional *trend* or direction of the weight curve; the second, the nutritional *state,* or weight of the baby as compared with what his weight should be at his age. One of the striking differences between a well nourished and a poorly nourished infant is the amount of subcutaneous fat. Is this in any way proportional to the blood fat? We have investigated this question.

Methods of Study.—The infants investigated were patients in the wards of the Boston Floating Hospital. Most of the patients in this hospital were under 1 year of age and suffering from disorders of nutrition rather than from acute illnesses. Some infants recovering from mild ailments and the infants of wet nurses gave us the necessary "normals" for comparison. It was through the courtesy of Dr. Henry I. Bowditch, medical director, and Drs. Paul W. Emerson and E. W. Barron, visiting physicians, that we were given the opportunity to study the patients from their respective services.

Blood was obtained by venous or sinus puncture, and the fat (total lipoids) determined by Bloor's nephelometric method.[3] "Fat" determined by this method includes the higher fatty acids whether originally combined as neutral fats, as lecithin, or as cholesterol esters, and in addition all of the cholesterol. No effort was made to separate these individual components, as it seemed likely that the desired information could be obtained as well from the total fat determination.

In all, fifty-two determinations of blood fat from forty-eight different infants were made. In Table 1 is given the essential information concerning each case, together with the results obtained.

In the column headed "Nutritional State" (Table 1) the letters refer to the state of nutrition as determined by a comparison between the weight of the infant and the average weight of normal infants of the same age. The infants were arbitrarily divided into four classes as follows:

Class A, 85 to 100 per cent. of average normal weight.
Class B, 70 to 85 per cent. of average normal weight.
Class C, 60 to 70 per cent. of average normal weight.
Class D, below 60 per cent. of average normal weight.

In the column headed "Nutritional Trend" the signs refer to the general direction of the weight curve at the time of taking of the blood sample. Infants gaining in weight are classed as +, those stationary as ±, and those losing —. Feeding formulas are expressed roughly in

3. Bloor, Walter R.: Jour. Biol. Chem., 1914, **17,** 377. Part of the analytical work was performed in Dr. Bloor's laboratory in the Department of Biological Chemistry of the Harvard Medical School. We are greatly indebted to Dr. Bloor for his aid and helpful suggestions.

TABLE 1.—DATA OF AUTHORS' CASES

No.	Age in Mos.	Weight Lb.	Weight Oz.	Nutritional State	Nutritional Trend	Feeding Fat	Feeding Carb.	Feeding Prot.	Calories per Kg.	Hours After Feeding	Blood Fat, per Cent.	Remarks
1	5	14	4	A	+	2.0	7.0	2.0	95	4	0.81	No disease
2	3	12	11	A	+	Breast fed			?	3	0.76	No disease
3	2	10	0	A	—	Breast fed			?	3	0.74	Syphilis; under treatment
4	18	21	4	A	±	0.0	4.5	3.2	45	3	0.66	Infectious diarrhea; convalescent
5	15	19	0	A	—	Buttermilk			65	4	0.66	Infectious diarrhea; acidosis
6	4	12	10	A	—	0.0	5.0	0.0	20	2	0.60	Intestinal indigestion; convalescent
7	18	21	0	A	—	Starving			0	12	0.57	Infectious diarrhea; acidosis
8	4	10	10	B	—	Starving			0	24	0.83	Severe diarrhea; acidosis
9	..	..	..	B	+	Breast fed			?	4	0.83	No disease
10	1	6	12	B	+	Breast fed			?	2	0.68	Syphilis; under treatment
11	6	13	4	B	—	Starving			0	36	0.67	Severe diarrhea; acidosis
12	10	14	6	B	—	0.0	5.0	0.0	50	2	0.52	Infectious diarrhea
13	2	7	9	B	—	1.2	5.4	1.0	65	2	0.52	Gastro-intestinal indigestion
14	1	5	14	B	—	Breast fed			?	4	0.60	Gastro-intestinal indigestion; mild
		5	7	C	+	Breast fed			?	4	0.77	Same child; recovered; week later
15	9	12	4	C	+	Breast fed			?	3	1.00	Pyelitis; convalescent
16	10	12	3	C	—	Starving			0	36	0.80	Severe diarrhea; acidosis
17	10	..	..	C	—	Starving			0	12	0.71	Severe diarrhea; acidosis
18	4	9	6	C	—	Starving			0	12	0.70	Severe diarrhea; acidosis
19	2	6	9	C	±	2.0	6.0	1.6	125	2	0.58	Intestinal indigestion; convalescent
20	3	7	8	C	+	2.0	6.0	1.6	125	3	0.64	No disease
21	1	5	14	C	+	1.4	6.0	1.2	100	3	0.64	Intestinal indigestion; convalescent
22	4	8	4	C	±	1.0	4.0	1.6	90	4	0.62	Syphilis; under treatment
23	2½	7	9	C	±	2.0	7.0	1.6	110	2	0.61	No disease
24	5	9	0	..	—	Protein milk			65	4	0.58	Intestinal indigestion
25	2½	6	14	C	±	Allm't mixte.			?	4	0.50	Intestinal indigestion
		7	0	C	+	Allm't mixte.			?	4	0.80	Same child recovered; week later
26	3	6	0	D	—	Starving			0	48	0.96	Severe diarrhea
27	4	8	7	D	—	Protein milk			40	2	0.71	Marasmus; nutritional edema
	4½	8	9	D	+	2.0	6.0	1.6	125	4	0.84	Same case; doing well
28	4	7	3	D	+	2.0	6.0	2.2	120	2	0.74	Syphilis; under treatment
29	11	12	0	D	—	2.0	6.0	1.6	100	4	0.73	No disease
30	3½	6	13	D	±	1.2	6.0	1.2	100	2	0.71	No disease
31	6	7	12	D	+	1.0	6.0	1.6	140	2	0.74	No disease
32	3½	7	7	D	±	2.0	6.0	1.6	110	2	0.71	No disease
33	2	5	14	D	—	Starving			0	12	0.52	Acute intestinal indigestion
	2½	5	5	D	—	1.0	5.0	1.2	90	4	0.70	Same case; recovering

TABLE 1.—DATA OF AUTHORS' CASES—(*Continued*)

No.	Age in Mos.	Weight Lb.	Weight Oz.	Nutritional State	Nutritional Trend	Feeding Fat	Feeding Carb.	Feeding Prot.	Calories per Kg.	Hours After Feeding	Blood Fat, per Cent.	Remarks
34	4	..	..	D	±	0.4	2.2	1.6	...	2	0.70	No disease
35	12	9	0	D	+	0.0	4.5	3.2	75	2	0.70	Intestinal indigestion; convalescent
36	2½	..	..	D	—	Starving			0	?	0.70	Marasmus; moribund
37	6	9	0	D	—	1.6	6.0	1.2	120	2	0.70	Mongolian idiot
38	12	12	8	D	±	Soft diet			120	4	0.70	Anemia pseudoleukemica
39	3	5	4	D	±	Breast milk			120	4	0.70	No disease
40	3	6	8	D	+	2.0	7.0	1.6	125	2	0.67	No disease
41	2	5	8	D	—	Dil. breast milk			70	2	0.64	Marasmus
42	1	4	12	D	±	1.6	7.0	1.2	120	2	0.64	No disease
43	11	10	8	D	—	0.0	4.5	3.2	70	2	0.62	Rickets
44	10	9	11	D	±	Protein milk			125	2	0.61	Intestinal indigestion
45	3	6	5	D	—	3.0	5.0	1.2	125	4	0.65	Intestinal indigestion; convalescent
46	5	7	15	D	—	Buttermilk			50	3	0.60	Intestinal indigeston
47	5	7	4	D	—	Protein milk			70	3	0.53	Intestinal indigestion
48	7	11	14	D	±	2.0	6.0	2.8	120	4	0.52	No disease

percentages. The total food intake, in terms of calories per kilo, appears in a separate column and serves to indicate the amount of each formula taken during the twenty-four hours.

As indicated in the table, blood samples were drawn two, three, or four hours after the last feeding, excepting, of course, the infants who were starving. With one or two exceptions the infants studied were on a four-hour feeding interval.

Comparing different infants falling in the same general nutritional class and on similar diets, we were unable to detect any differences in the blood fat that could be attributed to the time of taking of the samples. This is easy to understand when we consider that fat digestion and absorption in the infant is a relatively slow process. The stomach is often not emptied until three hours after a meal, and even when feeding is at four hour intervals, fat absorption from the intestine must be an almost continuous process. Conditions in infants are vastly different from those obtaining in the dogs studied by Bloor.[1] These animals were fasted and then fed on pure olive oil. The blood fat rose gradually and reached a maximum at the end of about six hours. Had the animals been fed every four hours, the curves would have been expected to overlap and approach a continuous line. Furthermore, our infants were fed only on rather low fat percentages and on small total amounts as compared to the dogs.

Inasmuch as the taking of the blood sample does not seem to influence the blood fat percentage, in subsequent classifications in this paper no particular attention will be taken of the time interval. Furthermore, in each class of children studied, blood samples were taken at intervals which averaged approximately the same, therefore eliminating any effect of the time interval.

Nutritional state and blood fat.—In Table 2 the results on blood fat are arranged in groups according to the nutritional condition of the infants.

From the results (Table 1) it is apparent that *blood fat is independent of the state of nutrition of the infant.* Subcutaneous fat does not necessarily bear any relation to circulating fat. This is not surprising, as fat in the tissues represents fat deposited at some past time. A well nourished baby with plenty of subcutaneous fat may be losing weight and not storing up any fat; on the other hand, a thin baby may

TABLE 2.—GROUPED BLOOD FAT PERCENTAGES

Nutritional State	A	B	C	D
Blood fat, per cent.	0.60, 0.74, 0.66, 0.81 0.66, 0.57, 0.76	0.83, 0.52, 0.52, 0.68 0.67, 0.60, 0.83	0.50, 0.80, 0.64, 0.80 1.00, 0.58, 0.71, 0.70 0.58, 0.64, 0.61, 0.77 0.62	0.70, 0.70, 0.73, 0.71 0.52, 0.70, 0.62, 0.58 0.70, 0.64, 0.74, 0.52 0.70, 0.74, 0.65, 0.71 0.84, 0.71, 0.67, 0.64 0.60, 0.61, 0.70, 0.96 0.70
Average	0.68	0.66	0.69	0.68

be laying on fat and have a blood rich in food fat on the way to the tissues. The important question in the nutrition of an infant is not so much whether he is fat or thin, but whether or not he is gaining weight.

Nutritional trend and blood fat.—Considering the infants studied from the standpoint of their weight curves, and dividing them into groups, it is seen that infants gaining show, on the average, a distinctly higher blood fat than those whose weight is stationary or who are losing. The results appear in Table 3.

Particularly interesting are the results obtained on the blood of the same infant during gaining and during stationary or losing periods. (Table 1, Patients 14, 25, and 27).

In Table 3 are included *all* blood fat determinations that we have made. It may appear better to eliminate those patients who were fasting. If this is done the average for the stationary group becomes 0.63, and for the losing group 0.64, figures essentially the same as those

obtained without eliminating the starving patients. In general, then, *an infant who is gaining weight, no matter what the state of his nutrition, will have a higher average blood fat than one who is not gaining.*

Blood fat and character of the feeding.—It is well known that infants are better able to "tolerate" the fat of breast milk than of cow's milk. If fat digestion and absorption are better when breast milk is fed, one might expect breast fed infants to show a high blood fat and

TABLE 3.—NUTRITIONAL TREND AND BLOOD FAT

Nutritional Trend	Gaining		Stationary	Losing
	Breast Fed	Artificially Fed		
Blood fat, per cent.	0.83, 0.77, 0.68 1.00, 0.80	0.64, 0.70, 0.81 0.74, 0.74, 0.84 0.64, 0.67	0.70, 0.50, 0.71, 0.66 0.64, 0.52, 0.58, 0.71 0.76, 0.61, 0.61, 0.70 0.70, 0.62	0.73, 0.80, 0.52, 0.70 0.60, 0.62, 0.74, 0.58 0.70, 0.83, 0.58, 0.52 0.66, 0.52, 0.70, 0.65 0.71, 0.71, 0.70, 0.57 0.64, 0.60, 0.67, 0.96 0.00
Average	(0.82)	0.76 (0.72)	0.64	0.66

a rapid gain in weight. In our group of infants who were gaining weight, those fed entirely, or in part, on breast milk showed an average blood fat percentage of 0.82, a considerably higher figure than any other group of infants in our series (Table 3). *Breast fed infants gaining weight have high blood fat percentages.*

As none of the infants studied was on "top-milk" mixtures, we are unable to state the effect on the blood fat of feeding artificial formulae with high fat percentages. We did have, however, a number of infants on formulae containing little or no fat, and these showed a lower average blood fat than any other group of cases studied (Table 4).

An infant on a fat-free diet is absorbing considerable food and hence there is not as great a demand on the fat deposits as during com-

TABLE 4.—INFANTS ON FORMULAE CONTAINING LITTLE FAT

Character of Feeding	Fat Free	Starvation	Acidosis
Blood fat, per cent.	0.70, 0.70, 0.62, 0.60 0.66, 0.66, 0.52, 0.60	0.80, 0.52, 0.70, 0.83 0.72, 0.70, 0.57, 0.67 0.96, 1.02	0.80, 0.83, 0.72, 0.70 0.67
Averages	0.63	0.75	0.74

plete starvation; at the same time no fat is being absorbed, so that conditions favor a low blood fat.

During complete starvation blood fat figures are relatively high (Table 4, second column), as might be expected. The significance of this has already been discussed.

The majority of the infants starved were suffering from severe diarrhea; the general symptomatology approaching the clinical picture of so-called "intoxication." Five of these infants showed definite evidences of acidosis; there was hyperpnea, a lowering of the carbon dioxid tension in the alveolar air, and a diminution of the alkali reserve. The acidosis was of the type described by Howland and Marriott.[4] that is, an acidosis not due to the acetone bodies. It is interesting to note that, as a group, these cases of acidosis showed no higher blood fat than the group of starving infants without acidosis of a significant degree. It has been shown by Gray[5] that in diabetes a high blood fat percentage usually occurs with acidosis. It would seem likely that in infants of the type described the failure of blood fat to rise may be due to the peculiar nature of the acidosis, it being of an entirely different origin from diabetic acidosis.

It is interesting to note that the average blood fat of the forty-eight infants that we have studied is somewhat higher than the results obtained from normal adults by Bloor.[6] He found an average blood fat of 0.59 as compared with our figures of 0.68. Blood from the adults studied was drawn before breakfast and therefore the effect of feeding fat was eliminated, and at the same time the fast was not of sufficient length to use up the carbohydrate stores to such a great extent as to call out much fat from the fat depots. The figures that Bloor obtained might be considered minimum rather than average for the twenty-four hours. A further explanation of the differences lies in the fact that the adult is usually in a state of weight equilibrium, whereas the normal infant is gaining. The infant ingests more fat per unit of body weight than the adult, and would therefore be expected to have constantly more fat in the blood stream on the way from the intestine to the liver and fat depots.

The fact that certain groups of infants show amounts of blood fat which vary distinctly from the general average of other groups suggests the desirability of further and more intensive work on special types of nutritional disorders from the standpoint of blood fat. It would be of especial interest to study further the particular group of cases in which failure to thrive has been attributed to difficulties in the digestion and absorption of fats.

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4. Howland and Marriott: Am. Jour. Dis. Child., 1916, **11,** 309.
5. Gray, H.: Boston Med. and Surg. Jour., 1918, **178**, 16.
6. Bloor: Jour. Biol. Chem., 1916, **25,** 577.

ACTIVE IMMUNIZATION OF INFANTS AGAINST DIPHTHERIA *

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The presence of diphtheria in civilized communities constitutes an important hygienic problem. It shows the need for a practical and efficient method of *active immunization,* that will protect the child and adult population. Such protection should be applied early in life, so that an efficient active immunity will be produced during that period when the individuals are most susceptible and the disease causes the greatest mortality; that is, from 1 to 5 years of age.

A. VITAL STATISTICS ON DIPHTHERIA

A short review of the tables furnished by vital statistics in this country, in England and in Germany will help to emphasize the foregoing statement, which is quite thoroughly realized by physicians in general, but especially by those engaged in public health work.

1. Morbidity Statistics.

TABLE 1.—MORBIDITY AND MORTALITY FROM DIPHTHERIA IN NEW YORK CITY DURING THE PAST FIVE YEARS

Year	Morbidity	Mortality
1913	14,535	1,333
1914	17,129	1,491
1915	15,259	1,278
1916	13,521	1,031
1917	12,624	1,158
Total for five years	73,068	6,291
Yearly average	14,613	1,258

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2. Mortality Statistics.

TABLE 2.—MORTALITY FROM DIPHTHERIA IN NEW YORK CITY FROM 1891 TO 1900

Age	Number	Per Cent.
Under 1 year	1,665	9.2
1 to 2 years	4,263	23.0
2 to 3 years	3,817	21.2
3 to 4 years	2,900	16.1
4 to 5 years	1,908	10.6
Under 5 years	14,553	81.5
5 to 10 years	3,052	17.0
10 to 15 years	241	1.3
Under 15 years	17,846	

TABLE 3.—TOTAL MORTALITY AND MORTALITY UNDER FIVE YEARS FROM DIPHTHERIA IN NEW YORK CITY FROM 1901 TO 1917

Year	Total Mortality	Under Five Years	Per Cent.
1900	1,920	1,354	70.0
1901	2,068	1,546	74.7
1902	2,015	1,503	74.5
1903	2,190	1,606	73.3
1904	2,084	1,566	75.1
1905	1,544	1,178	76.3
1906	1,908	1,476	77.7
1907	1,470	1,354	92.1
1908	1,758	1,404	79.8
1909	1,714	1,418	82.7
1910	1,715	1,324	77.2
1911	1,281	1,004	78.3
1912	1,125	873	77.6
1913	1,333	972	72.9
1914	1,491	1,143	76.6
1915	1,278	967	75.6
1916	1,031	795	77.1
1917	1,158	842	72.7
Total	29,873	23,150	77.5

TABLE 4.—Mortality from Diphtheria in the United States. U. S. Special Report, 1900 to 1904

Age	Number	Per Cent.
Under 1 year	3,736	7.0
1 to 2 years	8,001	15.0
2 to 3 years	7,990	14.8
3 to 4 years	7,207	13.5
4 to 5 years	5,989	11.0
Under 5 years	32,923	61.0
5 to 10 years	14,818	27.6
10 to 15 years	3,191	6.0
15 years up	2,628	5.0
Unknown	87	
Total	53,647	

TABLE 5.—Mortality Census from Registration Area in the United States for the Year 1910

	Deaths	Deaths per 100,000 Population
1. Diphtheria	11,512	21.4
2. Measles	6,508	12.3
3. Scarlet fever	6,255	11.6

TABLE 6.—Mortality from Diphtheria in the Registration Area of the United States. U. S. Census 1914 and 1915

Year	Number	Deaths per 100,000 Population
1914	11,786	17.9
1915	10,544	15.7

TABLE 7.—AGE INCIDENCE OF 2,711 CASES OF DIPHTHERIA ADMITTED TO BAGINSKY'S CHILDREN'S HOSPITAL IN BERLIN BETWEEN 1890-1897.

Age	Number of Cases	Per Cent. of Total of Cases	Number of Deaths	Death Rate per 100 Admissions	Death Rate at Each Age Period
0 to 6 months	15	0.55	4	0.15	26.6
6 to 12 months	69	2.50	36	1.32	52.2
1 to 2 years	227	8.30	110	4.06	48.4
2 to 3 years	317	11.60	119	4.30	37.5
3 to 4 years	354	13.05	121	4.40	34.2
4 to 5 years	337	12.40	84	3.09	24.9
5 to 6 years	264	9.70	61	2.25	23.1
6 to 7 years	280	10.30	61	2.25	21.8
7 to 8 years	209	7.70	26	0.95	12.4
8 to 9 years	175	6.40	23	0.84	13.1
9 to 10 years	146	5.30	19	0.70	13.0
10 to 11 years	101	3.70	9	0.33	8.9
11 to 12 years	80	2.90	8	0.29	10.0
12 to 13 years	65	2.40	7	0.25	10.8
13 to 14 years	72	2.65	6	0.22	8.3
Total	2,711		694		Av. 25.6

TABLE 8.—MORTALITY FROM DIPHTHERIA IN ENGLAND IN 1915

	Number	Deaths per 100,000 Population
All ages	5,895	16.6
Under 15 years (same age group)	.....	49.4

These rates are about the same as in 1914, when the mortality was heavier than in any previous year.

The following facts may be deduced from the tables given:

1. That the morbidity and mortality from diphtheria is quite high and constant, showing that (*a*) in spite of the extensive use of small prophylactic doses of antitoxin the total number of cases of diphtheria has not been reduced to any extent; (*b*) the measures taken at present in isolating and treating the temporary or more persistent carriers of diphtheria bacilli are of little benefit in accomplishing results on a large scale.

2. That children from 1 to 5 years of age are most susceptible to the disease and show by far the greatest mortality. In one table 81.5 per cent. of deaths, in another table 77.5 per cent., are shown to have

occurred under 5 years of age. As is well known, the dangerous laryngeal forms and the complicating bronchopneumonias are seen especially in this group of young children.

3. That the mortality from diphtheria is nearly as great as that from measles and scarlet fever combined.

4. That the yearly mortality from diphtheria in the United States calculated on the basis of the figures given in Table 5 is about 23,540 and the morbidity from this disease would be approximately ten times higher. Such figures present themselves in spite of the very valuable therapeutic remedy which we have in the form of antitoxin. It would therefore be of the greatest importance, considering these impressive statistics, to utilize to the fullest extent possible a method of active immunization that will render our total infant population, as well as the susceptible portion of our child and adult population, protected against this disease.

Recent investigations into the subject of natural and active immunity in diphtheria,[1] and studies with the Schick test,[2] a valuable clinical test at our disposal at the present time for determining diphtheria immunity, would seem to offer a solution to the problem of the control of diphtheria.

The tables give the results with the Schick test on various groups of children. Tables 9 and 21 are interesting as showing the very large proportion of positive reactions among children over 6 months of age.

The protection of the infant derived from the mother is only temporary and lasts about six to nine months after birth. Some children retain this maternal immunity for a year, and some are protected for even one and one-half years. The period of greatest susceptibility to diphtheria is between the first and fifth years of life. After the sixth

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B. THE SCHICK TEST

TABLE 9.—Results with the Schick Test

Age	Total	Negative	Positive	Per Cent. Positive
6 mo. to 1 year	10	5	5	50.0
1 to 2 years	68	22	46	67.6
2 to 4 years	273	93	180	65.9
4 to 6 years	249	116	133	53.4
6 to 8 years	196	123	73	37.2
8 to 15 years	237	171	66	27.8
Over 15 years	167	126	41	24.5
Total	1,200	656	544	45.3

See also Table 21, summary of Schick tests at the New York Foundling Asylum.

TABLE 10.—The Schick Test at the New York Catholic Protectory

Age	Total	Negative	Positive	Per Cent. Positive
4 to 6 years	126	113	13	10.3
6 to 8 years	212	202	10	4.7
8 to 10 years	91	82	9	9.9
10 to 15 years	233	220	13	5.5
15 years and up	25	24	1	4.0
Total	687	641	46	6.7

TABLE 11.—The Schick Test at the Institute of Mercy

Age	Total	Negative	Positive	Per Cent. Positive
4 to 6 years	62	54	8	12.9
6 to 8 years	62	52	10	16.1
8 to 10 years	47	41	6	12.7
10 to 15 years	151	141	10	6.6
Total	322	288	34	10.5

TABLE 12.—THE SCHICK TEST AT ST. JOSEPH'S INSTITUTE

Age	Total Tested	Immunes			Non-Immunes Positive	Per Cent. Positive	Per Cent. Pseudo
		Negative	Pseudo	Total			
a. (Boys)							
5 to 10 years	55	48	0	48	7	12.7	0.0
10 to 15 years	112	103	8	111	1	0.9	7.1
15 to 20 years	51	39	11	50	1	1.9	21.5
Total	218	190	19	209	9	4.1	8.7
b. (Girls)							
5 to 10 years	36	24	1	25	11	30.6	2.8
10 to 15 years	69	49	11	60	9	13.0	15.9
15 to 20 years	43	28	11	39	4	9.3	25.6
Total	148	101	23	124	24	15.5	16.2

TABLE 13.—THE SCHICK TEST AND CONTROL TEST AT THE DOMINICAN CONVENT

Age, Years	Total Tested	Immunes			Nonimmunes			Per Cent. Positive	Per Cent. Pseudo
		Negative	Pseudo	Total	Positive	Combined	Total		
4 to 6	52	29	8	37	14	1	15	28.8	15.4
6 to 8	67	46	14	60	6	1	7	10.4	20.8
8 to 10	32	13	12	25	4	3	7	21.8	37.5
10 to 15	71	42	25	67	2	2	4	5.6	35.2
Total	222	130	59	189	26	7	33	14.8	26.5

year the number of children showing a positive Schick reaction diminishes rapidly. Table 10 shows from 4 to 10 per cent. of positive reactors after the sixth year. Table 11 also shows a relatively small proportion of positive Schick reactions at this age (average 10.5 per cent.). Table 12 shows in a striking way that occasionally in an institution a group of 100 or more children over 10 years of age will be found, among whom only one or two may give a positive reaction. This will explain why diphtheria seems to be a relatively rare disease in some institutions, in which children from 7 to 15 years are congregated.

A prolonged experience extending over a number of years has shown to the writer the following important facts in connection with the Schick test and the active immunization with toxin-antitoxin:

1. The negative Schick reaction, when properly carried out with a suitable diphtheria toxin, indicates quite definitely the presence of immunity to diphtheria. This fact was conclusively demonstrated in our experience at the Willard Parker Hospital. During a period of over four years more than 1,200 patients suffering from scarlet fever were admitted to that institution, who gave on admission a negative Schick reaction. All the tests were made by the same observer, and the patients were carefully watched every day. None of these patients was immunized either actively or passively, and yet, even though from 15 to 20 per cent. became carriers of virulent diphtheria bacilli at one time or another during their stay in the hospital, not a single patient developed a true clinical diphtheria.

2. The negative Schick test is of value, not only in showing an immunity to diphtheria at the time the test is made, but also in indicating in children over 1½ to 2 years of age the *development* of a natural immunity, which seems to be *permanent*. This was quite definitely shown by making Schick retests on such children in the institutions in which we carried on our work in active immunization with toxin-antitoxin. Over 3,000 children, who had given a negative Schick reaction at the time of the first test, were retested at different intervals over a period of three years and the negative reaction was found to persist in almost all. From 1 to 2 per cent. gave a positive reaction at the retest, and these children can be regarded as borderline cases, who have a small amount of antitoxin that may show variations under different conditions.

3. In children below 6 to 9 months of age the immunity, as shown by a negative Schick reaction, is only temporary and derived from the mother through the placental circulation. In breast-fed infants antitoxic antibodies are also derived through the breast milk. Almost all these infants sooner or later become susceptible to diphtheria. Those whose mothers have no immunity of their own are susceptible

at birth, while most of the others, whose mothers are immune, become susceptible from six to nine months after birth. A few infants remain immune at 12 months, and an occasional child may remain protected by its maternal immunity even up to the eighteenth month. These facts came out very strikingly in our results at the New York Foundling Asylum. The results and the conclusions to which they lead in regard to the universal immunization of all children under 1 year of age or, to be on the safe side, under 1½ years of age, will be given further on.

4. The foregoing tables show that an increasing proportion of children gradually develop a natural immunity to diphtheria. In adult life the majority (85 to 90 and even 95 per cent.) have become immune. It is rather important to bear this fact in mind. It shows that by actively immunizing all children under 12 to 18 months, and only those children over 18 months who give a positive Schick reaction, we can render the child population immune to diphtheria and tide it over the period of greatest susceptibility. The following tables show that we can produce a lasting active immunity with diphtheria toxin-antitoxin in from 95 to 100 per cent. of susceptible individuals. This active immunity is shown by the fact that during subsequent exposure to the disease, the children remained free from diphtheria, and is also shown by our obtaining a persistent negative Schick reaction at later retests. This immunity has been found to last, now, over three years, and in a small group whom we had the opportunity of observing, over four years. These children will be retested further at yearly intervals to determine whether any number lose their active immunity. So far this has not been the case.

5. The character of the immunity produced by the injection of toxin-antitoxin may be either (*a*) an active immunity similar to that following other forms of vaccination, or (*b*) it represents the earlier development of a natural immunity that would have more gradually developed in these individuals in later years, or finally, (*c*) it represents a combination of these two factors. If it represented only the first type of immunity it would be likely only temporary and protect the child for about two or, at the utmost, only three years. If it repsented the second type, or natural immunity, it would be probably permanent. This is shown by the persistence for years of a negative Schick reaction in those children who are found naturally immune by the test. It is quite likely, however, that we are dealing with (*c*) a combination of these two factors. An active immunity is developed, and the tissue cells of the individuals are so sensitized that under subsequent conditions of exposure to the ubiquitous diphtheria bacillus they readily respond by producing a fairly large supply of antitoxin. This remains more or less constant in some, is found increased in others, and is

diminished slightly in still others. The following three tables represent determinations of the antitoxin content of actively immunized children. They show the amount of antitoxin produced and the variations in two examinations made at different times on the same persons.

C. ANTITOXIN DETERMINATION IN THE ACTIVELY IMMUNIZED

TABLE 14.—Two Antitoxin Determinations Made on Actively Immunized Children Six Months and Eleven Months after Two or Three Injections of Toxin-Antitoxin

(A) SHOWING A DIMINISHED OR A SIMILAR AMOUNT OF ANTITOXIN AT THE SECOND DETERMINATION

Number	Six Months, Units	Eleven Months, Units	Number	Six Months, Units	Eleven Months, Units
1	2.0	1.0	14	0.12	0.1
2	1.5	1.0	15	0.02	0.01
3	0.012	0.012	16	0.1	0.05
4	0.012	0.01	17	0.02	0.02
5	0.2	0.2	18	0.01	0.01
6	0.005	0.005	19	0.02	0.01
7	0.5	0.2	20	0.01	0.01
8	0.5	0.25	21	0.01	0.01
9	0.01	0.01	22	0.1	0.01
10	0.2	0.2	23	0.012	0.01
11	0.5	0.2	24	1.0	0.5
12	0.12	0.1	25	0.05	0.05
13	0.3	0.3			

(B) SHOWING AN INCREASED AMOUNT OF ANTITOXIN AT THE SECOND DETERMINATION

26	1.0	3.0	34	0.005	0.02
27	0.05	0.5	35	0.75	2.0
28	0.2	1.0	36	0.1	0.2
29	0.1	0.2	37	0.02	0.1
30	0.1	0.25	38	0.01	0.1
31	0.012	0.5	39	0.01	0.2
32	0.2	0.5	40	0.01	0.2
33	0.1	0.2			

The amount of antitoxin in Table 14 and in the following two tables represents units of antitoxin per cubic centimeter of serum. The determinations were made in the guinea-pig by a modification of Römer's intradermal test.

TABLE 15.—Relative Efficiency of Two and Three Doses of Toxin-Antitoxin

Units of Antitoxin in Blood Serum	Group 1 2 Doses, Each 1.0 C.c. Number Injected	Group 2 3 Doses, Each 1.0 C.c. Number Injected
0.01	7	9
0.02	2	8
0.05	1	0
0.1	1	6
0.2	3	6
0.5	2	5
1.0	0	5
2.0 up	0	1
Total	16	40
Total showing 0.1 unit and up	6	23
Per cent. showing 0.1 unit and up	37.5	57.5

The results in Table 15 show that a better antitoxin production takes place after three than after two injections of toxin-antitoxin.

The next table (Table 16) shows the persistence of the active immunity, as determined by the presence of antitoxin in the blood from fifteen to eighteen months after the injections of toxin-antitoxin.

TABLE 16.—Antitoxin Content of Actively Immunized Children Fifteen to Eighteen Months after Toxin-Antitoxin Injections

Units of Antitoxin	Institution			Total
	St. Dominic	Leake and Watts	St. Agnes	
0.005	7	4	..	11
0.01	5	13	..	18
0.02	8	7	..	15
0.05	16	5	..	21
0.1	9	5	7	21
0.2	13	13	1	27
0.5	15	16	13	44
1.0	2	1	13	16
2.0	4	2	7	13
4.0	3	2	9	14
8.0	5	1	0	6
Total	87	69	50	206
Total showing 0.1 unit and up	51	40	50	141
Per cent. showing 0.1 unit and up	58.6	60.0	100.0	53.9

Table 16 shows that a fairly large proportion of the immunized children have a considerable amount of antitoxin even as late as eighteen months after the injections of toxin-antitoxin.

D. ACTIVE IMMUNIZATION WITH DIPHTHERIA TOXIN-ANTITOXIN

The following tables show the immunizing results obtained with toxin-antitoxin, as determined by subsequent retests with the Schick reaction.

TABLE 17.—RETESTS AFTER ACTIVE IMMUNIZATION

(A) SUMMARY OF RESULTS OF ACTIVE IMMUNIZATION WITH DIPHTHERIA TOXIN-ANTITOXIN IN VARIOUS INSTITUTIONS

Institution	Total Tested	Doses of Toxin-Antitoxin	Months After Injections	Schick Results	Retest, Per Cent. Negative
1. St. Agnes	54	1 and 2	12	50— 4+	92.5
2. St. Dominic	83	2 and 3	12	82— 1+	98.5
	19	1	4	13— 6+	68.4
3. N. Y. Juvenile Asylum	82	3	12	80— 2+	97.8
4. St. Joseph's	55	2 and 3	10	55—	100.0
	18	1	10	15— 3+	84.7
5. House of Refuge	72	2 and 3	2.5	66— 6+	91.6
	56	1	2.5	48— 8+	85.7
6. Hebrew Inf. Asylum	48	2	4	43— 5+*	89.8
	28	1	4	24— 4+*	85.7
7. Hebrew Orph. Asylum	117	1	8	95— 22+	81.2
8. Leake and Watts	43	2 and 3	6	43—	100.0
	7	1	2.5	3— 4+	42.8
9. Colored Orph. Asylum	91	3	3	42— 49+	46.1
		750 units antitoxin			
10. Skillman	150	2	2.5	142— 8+	94.6

* Received three more injections of toxin-antitoxin at this time. Schick retest at 10 months negative in all children.

(B) FINAL RESULTS IN ACTIVELY IMMUNIZED CHILDREN

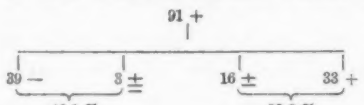
1. St. Agnes	20	1	20	18— 2+	90.0
	25	2	20	25—	100.0
	12	1	8	5— 7+	41.6
2. St. Dominic	41	2	25	41—	100.0
	43	3	25	43—	100.0
3. St. Joseph's	19	2	25	19—	100.0
	39	3	25	39—	100.0
4. Leake and Watts	49	3	17	48— 1+	98.0
	15	3	6	11— 4+	73.3
5. Colored Orph. Asylum	68	3*	14	38— 20+	55.7
6. Institute of Mercy	29	3†	12	28— 1+	96.6

* Received 750 units of antitoxin with first dose of toxin-antitoxin.
† Received 1,000 units of antitoxin with second dose of toxin antitoxin.

Table 17 shows the results of retests made from two and one-half to twenty-five months after the toxin-antitoxin injections. It shows in a striking way the high percentage of immunes, who received two or three injections of toxin-antitoxin. One injection was not as effec-

tive as the repeated injections. At the Colored Orphan Asylum we gave, in addition to the first dose of toxin-antitoxin, a prophylactic injection of 750 units of antitoxin. There was a small outbreak of diphtheria in the institution, which rendered it desirable immediately to protect the susceptible children. Table 18 gives the results in detail. It is interesting to see that a much smaller number of children became successfully immunized, thus showing a distinct interference by an excess of antitoxin with the efficient immunizing action of toxin-antitoxin.

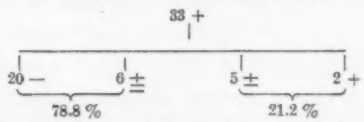
TABLE 18.—Results of Combined Active and Passive Immunization at the Colored Orphan Asylum



Schick retest made at three months. Three doses of toxin-antitoxin, each 1 c.c.; 750 units antitoxin with first dose.

In another institution, the Institute of Mercy, 1,000 units of antitoxin were given with the second injection of toxin-antitoxin. Table 19 gives the results of the first Schick retest.

TABLE 19.—Results of Combined Active and Passive Immunization at the Institute of Mercy

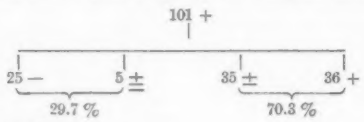


Schick retest at two and one-half months. Three doses of toxin-antitoxin, each 1 c.c.; 1,000 units of antitoxin with the second dose.

In this institution also the administration of an excess of antitoxin with the second dose of toxin-antitoxin has also interfered, though not to the same extent, with the efficiency of the immunizing response.

The active immunity following injections of toxin-antitoxin develops rather slowly. Such immunization alone, therefore, is unsuitable during a sudden, acute outbreak of diphtheria, when a considerable number of children have been exposed to the infection and have become carriers of virulent diphtheria bacilli. The danger from the disease to the non-immunes under such conditions is imminent. A combination of active and passive immunization of all positive Schick reactors would be indicated, to be followed by retests with the Schick reaction at the end of four to five weeks. If any of the children continue to give a positive reaction, showing that they had failed to become immune, they should receive three more doses of toxin-antitoxin at weekly intervals.

TABLE 20.—TIME OF DEVELOPMENT OF ACTIVE IMMUNITY AFTER TOXIN-ANTITOXIN INJECTIONS



Schick retest at three weeks.

FURTHER SCHICK RETESTS ON THOSE WHO HAD SHOWN A POSITIVE REACTION AT THREE WEEKS

Number Positives Left	Time (Weeks)	Result
43	4	2— 6± 35+
19	5	6— 13+
10	7	4— 6+
3	9	1— 2+
2	11	1— 1± —

Table 20 shows a group of 101 children who were admitted to the scarlet fever pavilion of the Willard Parker Hospital. On admission they gave a positive reaction and were actively immunized with three doses, each 1.0 c.c., of toxin-antitoxin. A Schick retest was made at three week (one week after the third injection of toxin-antitoxin) and subsequently at weekly intervals during the remainder of their stay in the hospital. A certain number of patients were discharged from the hospital at the end of their period of quarantine, so that all children could not be retested to the end of three months. Yet the table shows clearly that the protection, while it develops slowly, is yet successful in most of the children. From the table it can be seen that at three weeks, of the 101 children, 30 had become immune, 71 still showing a positive Schick reaction. At four weeks, of the 71, 43 were left at the hospital, and of these 8 more gave a negative reaction. At five weeks, of the 35 non-immunes, 19 were left, and of these, 6 gave a negative Schick test. At seven weeks, of the 13 non-immunes, 10 were left, and of these, 4 gave a negative test. It can thus be seen that of the non-immunes that we were able to retest, the majority finally showed antitoxin production in from five to seven weeks after the first injection of toxin-antitoxin.

The toxin-antitoxin mixtures used for immunization should be slightly toxic and represent about 85 per cent. of an L+ dose of toxin to each unit of antitoxin. The mixture should be prepared with a strong diphtheria toxin, so that each dose of 1 c.c. of the finished mixture will contain at least two and one-half almost neutralized L+

doses of toxin. Such mixtures may be prepared from a stronger toxin, so as to contain as high as five L+ doses, but a weaker toxin should not be used in its preparation. The mixture should be first tested in the guinea-pig by injecting 5 c.c. subcutaneously. The result should be a local induration and late paralysis, but not acute death of the animal.

E. OBSERVATIONS ON MATERNAL IMMUNITY TO DIPHTHERIA IN YOUNG INFANTS, AND ACTIVE IMMUNIZATION WITH TOXIN-ANTITOXIN

The following tables represent the results of studies at the New York Foundling Asylum on the duration of maternal immunity in young infants and on the efficiency of the immunization with toxin-antitoxin in infants and mothers, who gave a positive Schick reaction.

TABLE 21.—SUMMARY OF SCHICK TESTS BY AGE GROUPS

Age	Total	Negative	Positive	Per Cent. Positive
0 to 6 months	101	82	19	18.7
6 to 12 months	84	40	44	52.3
1 to 2 years	52	28	24	46.1
2 to 4 years	127	82	45	35.4
4 to 6 years	108	88	20	18.5
6 to 8 years	25	22	3	12.0
Total	497	342	155	31.2

Table 21 shows that the largest proportion of positive Schick reactions was found between the ages of 6 months and 4 years. The positive reactions diminish rapidly after the fourth year of life.

TABLE 22.—SUMMARY OF SCHICK TESTS AND OF CONTROL TESTS WITH HEATED TOXIN ON CHILDREN AND ADULTS

Age	Total Tested	Immunes			Nonimmunes			Per Cent. Positive	Per Cent. Pseudo
		Negative	Pseudo	Total	Positive	Combined	Total		
Children 0 to 8 years	519	354	23	377	140	2	142	27.3	4.4
Adults.....	113	59	43	102	6	5	11	9.7	38.0
	632			479			153		

In Table 22 it is interesting to note the relatively small number of pseudoreactions in children up to 8 years of age (4.4 per cent.), and the relatively large number in adults (38.0 per cent.), as compared with the positive Schick tests, of which the children (27.3 per cent.) have nearly three times as many as the adults (9.7 per cent.

TABLE 23.—COMPARATIVE RESULTS WITH SCHICK TEST IN MOTHERS AND INFANTS

Ages of Infants, Months	A Mother Neg. Infant Neg.	B Mother Neg. Infant Pos.	C Mother Pos. Infant Pos.	D Mother Pos. Infant Neg.
Up to 3	18	1	4	0
3 to 6	19	2	2	0
6 to 9	9	11	1	0
9 to 12	2	10	0	0
12 to 15	4	6	0	0
15 to 24	2	2	0	0
Total	54	32	7	0

Table 23 shows the following interesting points:

(*a*). The antitoxin immunity of the infant obtained from the immune mother lasts for about six to nine months after birth. Column A shows that thirty-seven out of fifty-four, or 68.5 per cent., had a negative Schick test during the first six months of life. The negative reaction in the nine children between 6 and 9 months of age is probably also due to a continuation of the passive immunity derived from the mother, while in the remaining eight children we may or may not be dealing with such an immunity. Only repeated Schick tests at later intervals could determine this point. The children who were still passively protected would lose their antitoxin in the course of the next few months, and then give a positive reaction; while those whose negative Schick reaction indicated an early developed natural immunity would continue to show a negative reaction.

(*b*). Column B shows that a large proportion of children belonging to immune mothers have positive Schick tests after the sixth month of life. Twenty-seven out of thirty-two children between 6 and 15 months, or 84.3 per cent., gave a positive Schick reaction.

(*c*). In Column C seven children are shown who gave a positive reaction and whose mothers also gave a positive reaction to the Schick test. The results indicate definitely that where a mother has no immunity, none will be present in her infant, if it is below 6 months of age.

(*d*). Column D shows that no case was found in which the mother had a positive and her young infant a negative Schick reaction. It was, of course, to be expected that where the mother had no immunity, none would also be found in her infant.

TABLE 24.—SCHICK TEST AND RETEST AT 6 5 MONTHS IN MOTHERS AND INFANTS. ACTIVE IMMUNIZATION WITH TOXIN-ANTITOXIN

Group 1 No.	Mother Immune			Infant Immune				
	Mother	Test 2/5	Retest 8/21	Infant	Age	Test	Age	Retest
1	A. G.	Ps. —	Ps. —	A. G.	1 mo.	—	7 mo.	+
2	L. W.	Ps. —	Ps. —	F. W.	4 mo.	—	11 mo.	+
3	A. S.	Ps. —	Ps. —	J. S.	5 mo.	—	12 mo.	++
4	B. S.	—	—	A. S.	6 mo.	—	12 mo.	±
5	A. C.	—	—	J. C.	4 mo.	—	11 mo.	+
6	B. C.	Ps. —	Ps. —	R. C.	5 mo.	—	12 mo.	—*
7	M. C.	Ps. —	Ps. —	C. C.	6 mo.	—	13 mo.	+
8	M. L.	—	—	M. L.	5 mo.	—	12 mo.	—
9	C. B.	—	—	H. H.	2 wk.	—	7 mo.	±
10	C. M.	—	—	E. M.	3 mo.	—	10 mo.	+
11	W. F.	—	—	R. F.	2 mo.	—	8 mo.	+
Group 2	Mother Immune			Infant Susceptible. Toxin-Antitoxin				
12	J. E.	—	—	M. E.	8 mo.	++	14 mo.	—
13	M. R.	—	—	G. R.	8 mo.	+	15 mo.	—
14	S. C.	Ps. —	Ps. —	J. C.	6 mo.	+	13 mo.	—
15	R. K.	Ps. —	Ps. —	E. K.	7 mo.	+	14 mo.	—
16	C. C.	Ps. —	Ps. —	T. C.	6 mo.	+	13 mo.	—
Group 3	Mother Susceptible Toxin-Antitoxin			Infant Susceptible. Toxin-Antitoxin				
17	M. M.	+	—	E. M	1 mo.	+	7 mo.	—
18	G. W.	Ps. +	Ps. —	E. W.	6 wk.	+	7 mo.	—
19	A. W.	Ps. +	Ps. —	A. W.	5 mo.	+	12 mo.	—
20	V. P.	+	—	G. P.	5 mo.	+	12 mo.	—

Ps. — = Pseudoreaction in an immune mother.
Ps. + = Pseudoreaction and positive reaction or combined reaction in a susceptible mother.
* Marasmus.

Table 24 shows in a striking way the following points:

1. In Group 1 there are eleven mothers and their infants, both of whom gave a negative Schick reaction at the time of the first test. The age of the infants at this time was 6 months or under. When

retested 6.5 months later, all but two of the infants gave a positive Schick reaction. One of the two (No. 6) was marasmic at the time of the retest. No. 4 was slowly losing its maternal immunity at 12 months, No. 7 was beginning to lose it at 6 months and had completely lost it at 13 months. No. 9 was just beginning to lose its maternal immunity at 7 months.

This group as well as the following two groups also show that the infant does not inherit the hypersensitiveness of the mother to the bacillus protein, which she shows in the form of pseudoreactions.

2. In Group 2 there are five mothers who were immune and gave a negative Schick reaction. Their infants, 6 months of age or over, were susceptible and gave a positive reaction. The infants were actively immunized with three doses, each 0.5 c.c. of toxin-antitoxin. At the retest 6.5 months later all gave a negative Schick reaction, thus showing that they had been successfully immunized.

3. In Group 3 there are four susceptible mothers whose young infants were also susceptible. All gave a positive Schick reaction at the primary test. To the mothers three doses of toxin-antitoxin, each 1 c.c., were given; to the infants three doses, each 0.5 c.c. At the retest, 6.5 months later, both the mothers and their infants gave a negative Schick reaction, thus showing that they had all become actively immunized.

4. The table shows very definitely that almost all infants, if they are not already susceptible at birth, become susceptible to diphtheria within the first year of life. Only a few infants retain their maternal immunity after the twelfth month, and probably all lose it before the eighteenth month of life.

5. The results show the efficiency of the active immunization with toxin-antitoxin.

6. From the table it can also be seen that a large proportion of mothers, ten out of twenty, gave a pseudoreaction. These pseudoreactions are best determined[3] by making a control test on the opposite forearm with a dilution of diphtheria toxin which has been heated at 75 C. for five minutes. In the control dilution 50 per cent. more of the heated toxin is used; the excess is added to allow for any possible deterioration that may have taken place in the bacillus protein during the heating process. It is this substance which causes the pseudoreactions.

7. The toxin-antitoxin injections produced *very little local or con-*

3. Zingher, Abraham: The Pseudo-Reaction in the Schick Test and Its Control, Jour. Am. Med. Assn., 1916, **66,** 1617. Zingher, Abraham: The Schick Test among Troops of the National Army, Jour. Am. Med. Assn., 1918, **70,** 227.

stitutional disturbances in these young infants. It is this freedom also from any marked reactions to the injections that makes the immunization in early life a very desirable procedure. Some of the mothers, especially those showing pseudoreactions, had rather severe local and constitutional symptoms, consisting of redness, swelling and tenderness of the arm, headache and slight febrile disturbance, lasting about two days. This susceptibility of older individuals is due, as stated before, to the bacillus protein contained in the mixture.

SUMMARY AND CONCLUSIONS

1. *All infants below 12, and if possible below 18, months of age should be actively immunized with three doses, each 1.0 c.c., of toxin-antitoxin. These injections should be given irrespective of the Schick test the infants may show at the time of immunization.* The injections are given subcutaneously in the arm or below the angle of the scapula, and repeated every seven days. The toxin-antitoxin is well tolerated by young infants, and for that reason the dose advised is the same as that given to older children. The relatively larger dose of toxin-antitoxin will, of course, also give rise to a better immunizing response.

2. All children over 18 months of age, as well as all youths and adults, should be tested with the Schick reaction first, and only those giving a positive reaction immunized with toxin-antitoxin. Three injections, each 1.0 c.c., are given subcutaneously, one week apart.

3. In infants below 18 months of age the Schick test is not a necessary part of the immunization, since all the infants should be actively immunized. By omitting the Schick test the procedure is greatly simplified for many general practitioners, to whom the test even now appears as a difficult and complicated procedure. The greater part of the most effective prophylaxis against diphtheria still remains in the hands of the general practitioner, and it will be only by getting his interested cooperation in this work and facilitating the process of immunization for him, that results of any magnitude will be achieved. Whenever possible, however, it will be of scientific interest to apply the Schick test to the infants as well as to the older children and adults.

4. The toxin-antitoxin mixture should be prepared in a reliable laboratory and carefully tested for potency in the guinea-pig before it is sent out for use. The mixture used should be slightly toxic and should represent about 85 per cent. of an L+ to each unit of antitoxin. It is important that the toxin-antitoxin should be supplied free of charge to physicians by municipal and state departments of health, so that immunization on a large scale will be carried out. For the

Schick test the outfit[4] devised by the writer will be found very convenient.

5. Improvements in the method of immunization are possible, and further work is being carried out at present especially to see whether a single dose of toxin-antitoxin will give in a considerable number of these infants results as good as those obtained with three doses. This would undoubtedly simplify the process and make it very convenient for general use. Our own results with single doses in a limited number of children have not shown as high a percentage of successful immunizations as those obtained by multiple injections.

6. The active immunization against diphtheria should be carried out first of all by the private physicians in the different homes, where a majority of the infants can be reached. In larger centers of population the milk stations, day nurseries, children's dispensaries, infant and orphan asylums furnish large groups of children suitable for immunization. The children of preschool age found in kindergartens and those of school age should be tested first with the Schick reaction, and those giving a positive test actively immunized. Whether such procedure can be made compulsory in the schools will depend on the enlightenment of the community, in which the work is to be carried out. Adults, especially those frequently or constantly exposed to diphtheria, such as doctors, nurses, hospital orderlies and patients in contagious disease hospitals, should also be tested with the Schick reaction and those giving a positive reaction actively immunized.

7. Finally, it may be stated that the diphtheria problem would seem nearer a solution now by the thorough application of these newer diagnostic and immunizing procedures, which should be encouraged by the various departments of health.

This work was carried out under the direction of Dr. William H. Park, Director of the Research Laboratory of the New York City Department of Health. His interest in the problem of diphtheria has been a great stimulus in continuing this study over a period of years.

The Research Laboratory will supply at a very reasonable price the toxin-antitoxin for immunization and the toxin for the Schick test. Where necessary the material will be supplied free of charge on condition that full reports will be sent in on blanks furnished by the laboratory. The toxin-antitoxin can now also be obtained from Parke, Davis & Co.

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4. Zingher, Abraham: A Simple Outfit for the Distribution of Diphtheria Toxin for the Schick Test, Jour. Am. Med. Assn., 1915, **65**, 329.

INFANTILISM, WITH TWO CASES OF THE BRISSAUD AND THE FRÖLICH TYPES, RESPECTIVELY *

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The subject of infantilism has come in recent years into ever increasing prominence. The term should be applied not only to adolescents or adults who possess in some degree the bodily and often the psychic characteristics of infancy, but to children of any age in whom there is a persistence of characters, especially sexual, which belong to a period of life decidedly earlier than the actual age of the patient. Further, a sharp distinction should be drawn between infantilism and nanism. There may be dwarfs who are in no respects infantile, such as those of a rachitic or achondroplastic nature. As Hastings Gilford[1] has pointed out, there has been in them an arrest of *growth*, but not of *development*. Less often there may be cases of infantilism which are the reverse of being dwarfs, as in one of the instances which I desire to record.

Much confusion still exists, however, in the classification of forms of infantilism. That proposed by Hastings Gilford[1] is worthy of serious consideration. The cases are divided by him into the essential forms, including ateleiosis and progeria; and the symptomatic forms, including the Lorain and the Brissaud types. Other forms of symptomatic infantilism have been described; among them the intestinal, pancreatic, pituitary, renal, cardiac and lymphatic forms.

It is not the intention, however, to review the subject at length in this connection, but merely to report two instances of the Brissaud and the pituitary types, respectively. They are put on record not only on account of their intrinsic interest, but because in some respects they were studied with considerable care.

REPORT OF CASES

CASE 1.—Mary G., aged 7 years, Italian, entered the children's ward of the hospital of the University of Pennsylvania, Jan. 23, 1912. The family history was negative, the parents and grandparents having been apparently normal in development. Five other children were living and well and in normal condition. The father had some asthma, but in other respects had good health.

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* Read at the Annual Meeting of the American Pediatric Society, Lenox, Mass., May, 1918.

1. Gilford, Hastings: Lancet, London, 1914, **1**, 587.

The child was well during infancy and breast-fed up to the age of 21 months. When 1½ years old she had a severe attack of whooping cough lasting six months, exhibiting spasms of coughing in which she would often fall to the floor, "looking as if she were dead." Since that time she is said not to have grown any physically, although mentally the parents think she is normal. She frequently cries and complains of pain before rain or damp weather. She also appears to be a trifle weak in her legs at times. A year prior to admission she was examined by Dr. J. W. McConnell of the Department for Nervous Diseases, who found the mental condition apparently normal.

Examination.—A well nourished Italian child. The extremities seem short for the size of the thorax, and the legs are slightly bowed. The skin is harsh and dry, with a tendency to gooseflesh. The child talks plainly and coherently, answering questions rationally, as far as can be determined, but she speaks chiefly Italian. She seems strong for her size, but walks with a slight wabbling gait. Her weight is 20 pounds (normal for the age, 49 pounds); her height 29 inches (normal for the age, 45 inches). Expressed relatively, this child at 7 years has the weight belonging to one of 10 months, and the height of one of 20 months. The head is rather large and well formed; the hair short and slightly dry and harsh. No enlargement of the cervical lymphatic glands is noted, nor any rigidity of the neck. The eyes are somewhat far apart; the palpebral fissure narrowed, but without slanting of the eyes. The tongue appears slightly larger than normal, but does not protrude. Examination of the nose, ears and pharynx gives negative results. The thyroid gland cannot be palpated, and this region in the neck does not seem to be as full as in normal children. The chest is short and full. There are slight subcutaneous fatty deposits in the supraspinous fossae. There is no enlargement of glands in the axilla. The heart and lungs appear to be normal; there is no beading of the ribs; the abdomen is much distended, resulting in a distinct costal flare, and producing a compensatory lordosis of the lumbar spine; no masses can be felt in the abdominal cavity; the spleen cannot be felt, and the liver is not enlarged. Nothing wrong is discoverable in the extremities other than the shortness and bowing referred to.

January 24 measurements were taken of different parts of the body, contrasting these with similar measurements of a boy of the same age in the hospital at the time. The measurements of the patient were taken again on June 7, and are shown in the third column in the tabulation.

MEASUREMENTS

	Normal Boy, Jan. 24, Inches	Marie, Jan. 24, Inches	Marie, June 7, Inches
Height	48	29	30¼
Dorsal spine to iliac crest	11½	8	8½
Dorsal spine to floor	38	21½	22½
Anterior superior spinous process to external condyle	13¼	7¼	7¾
Anterior superior spinous process to external malleolus	24	13¼	14
Arms	15½	8	8½
Hands	5½	3½	3¾
Fingers	2½	1¾	1¾
Suprasternal notch to symphysis	15½	11	11½
Suprasternal notch to floor while standing	39	21	23¾
Suprasternal notch to glabella	18¾	15¼	17½

The contrast in size is well shown in the accompanying photograph (Fig. 1).

The patient while in the hospital was cheerful, active, and seemed to be of good mentality, as far as could be judged in a child of foreign parentage with a limited knowledge of English. The temperature averaged somewhat below

normal—from 97.5 to 98 F. She was troubled at times with cough, which yielded to treatment, and early in June it was noticed that she was perspiring a good deal about her head. Apparently she did not have this condition earlier, and it may have been the result of treatment. The bowels were regular, formed or soft, brownish in color. Bacteriologic examination made on June 9 showed the stools negative for *Bacillus bifidus, Bacillus infantilis,* coccal and fermentative forms. Roentgen-ray examination of the body made by Dr. Henry K. Pancoast revealed nothing abnormal. The blood examined on admission gave hemoglobin, 58 per cent.; red blood corpuscles, 3,440,000; leukocytes, 11,000; with polymorphonuclears, 69 per cent., and lymphocytes, 21 per

Fig. 1.—Infantilism of Brissaud type; patient beside a normally developed boy of the same age.

cent. The last examination, on June 9, showed hemoglobin, 70 per cent.; red blood corpuscles, 4,000,000; leukocytes, 8,000, with polymorphonuclears, 36 per cent., and lymphocytes, 45 per cent. Examination of the urine made on several occasions showed a faint trace of albumin, and at times a few cylindroids and casts, but no indication of any disease of the kidneys.

Thyroid extract was first administered in doses of one-half grain three times a day, and continued until March 31, when it was increased to 1 grain three times a day. This was persisted with until May 3. Meanwhile there had been at first a moderate loss in weight, followed by a slight gain; so that on May 3

she had lost in all about a pound. There had been, meantime, a slight but noticeable increase in the size, as is shown in the measurements taken on June 7. On May 3 the thyroid extract was discontinued and pituitary extract given until May 27 in doses of 1 grain three times a day. She left the hospital June 16 weighing 21 pounds.

This case was at first supposed to be intestinal infantilism, and the provisional diagnosis to this effect was recorded on the case-history. Further study seemed, however, to negative this diagnosis. There was not the general poor health, emaciation, anemia and disturbance of the gross character of the stools seen in this disease; and bacteriologic examination of the feces showed, as stated, an absence of the *Bacillus*

Fig. 3.—Pituitary infantilism.

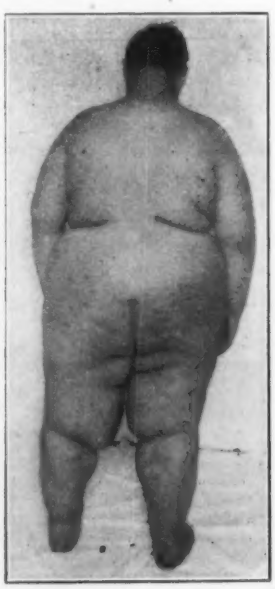

Fig. 2.—Pituitary infantilism.

bifidus, Bacillus infantilis and coccal forms, which, according to Herter, are present in intestinal infantilism. On the other hand, certain features existed which were very suggestive of infantilism of the Brissaud type. There were, namely, the moderate harshness of the skin, the bowing of the legs, the prominent abdomen, the moderate deposits of fat over the scapulae, and the like, all of which pointed to a hypothyroidism; not, it is true, of a degree to produce cretinism, but at least to make the subject cretinoid. The roentgen examination reported negative findings. Certainly there was nothing of a nature about them to suggest achondroplasia, nor were there, indeed, any other symptoms characteristic of this affection.

CASE 2.—John S., aged 11 years; admitted to the Children's Ward of the Hospital of the University of Pennsylvania, Feb. 7, 1915, for excessive obesity. The parents stated that the tendency to the undue deposit of fat had been noticed since the age of 11 months. This had been gradually progressing and did not seem to be influenced by diet. The health in other respects had been good, and his mental capacity rather above the average, they thought. He had always indulged in a fair amount of exercise. The father said that the boy had had a fall when 14 months old, to which he attributed the existence of a limp. Both parents are stout, but not to any abnormal degree; one brother and one sister said to be "plump," but not excessively fat.

Examination.—The boy is unusually large for his age (Figs. 2 and 3), and excessively obese. The breasts are large, apparently from deposit of fat; the thyroid gland cannot be felt; there is nothing abnormal about the heart, lungs, or abdomen. He appears to have the full intelligence of a boy of his age. The following measurements were taken: height, 5 feet 1 inch (normal for age,

Fig. 4.—Pituitary infantilism; roentgenogram of skull showing small sella turcica.

4 feet 5 inches); weight, 251 pounds (normal for age, 70 pounds); circumference at nipples. 45½ inches; just below this, 44 inches; at umbilicus, 47 inches; at anterior superior spinous processes, 51 inches; of left thigh, 34 inches; right thigh, 33 inches; calves, 21 inches; ankles, 11 inches; arms, 15½ inches; left forearm, 12 inches; right forearm, 12½ inches; left wrist, 8 inches; right wrist, 7½ inches. In brief, this boy at 11 years has the height of one of between 14 and 15 years, and a weight beyond that of a normal man.

The boy walks with a distinct limp. The abdomen is very pendulous. The penis is buried in fat, but seems to be small for his age and very small for the rest of his development. The testicles are descended, but are very small. There is almost no trace of pubic hair.

The blood contained 4,740,000 red blood cells; 8,600 leukocytes; 80 per cent. hemoglobin; polymorphonuclears, 76 per cent.; lymphocytes, 19 per cent.; large mononuclears, 4 per cent.; eosinophils, 1 per cent. The urine shows specific gravity, 1.022; slight trace of albumin; no formed elements. Dr.

Henry K. Pancoast made a roentgen-ray examination of the head (Fig. 4) and reported "sella turcica definitely smaller than normal, indicating a small pituitary body." An examination for the sugar tolerance made by Dr. A. H. Hopkins on February 12 resulted as follows: preformed sugar, 0.084; 100 gm. of glucose given by mouth showed:

½	hour	after	blood-sugar = 0.088
1	hour	after	blood-sugar = 0.104
1½	hours	after	blood-sugar = 0.090
2	hours	after	blood-sugar = 0.090
3	hours	after	blood-sugar = 0.106
4½	hours	after	blood-sugar = 0.086

No glycosuria occurred throughout.

A test for sugar tolerance was again made by Dr. Hopkins on April 19, after continued administration of pituitary extract during two months. This gave: preformed sugar, 0.060; 100 gm. of glucose given by mouth:

½	hour	after	blood-sugar = 0.110
1	hour	after	blood-sugar = 0.189
1½	hours	after	blood-sugar = 0.2
2	hours	after	blood-sugar = 0.151
3¼	hours	after	blood-sugar = 0.142

Fehling's solution was decolorized at the end of 1 hour, 1½ hours and 2 hours. The test showed marked reduction in the sugar tolerance after the administration of pituitary extract. Examination by Dr. Edward Martin indicated that the limp in the left leg depended probably on a coxa vara.

The patient was given a low carbohydrate diet in limited amounts. On March 12 he was ordered a special diet of known quantities, starting with four eggs (180 gm.), milk (1,000 c.c.), cream (50 c.c.), bread (200 gm.), butter (50 gm.), cream of wheat (200 gm.), sugar (16 gm.). This was varied from time to time to a slight extent, and meanwhile the child was made to exercise systematically in the hospital gymnasium. It is likely that he did not confine himself strictly to his diet, but ate other articles surreptitiously. In any event he was taken home May 30, having lost only 17 pounds.

This case represents an excellent instance of the hypopituitarism of Fröhlich, except in certain particulars. The infantile character of the sexual organs, the great obesity and its distribution, the tolerance for carbohydrates are positive indications. On the other hand, the subjects of Fröhlich's syndrome often exhibit a retarded skeletal development, while the case now reported possessed a decided overgrowth. This may depend, as Cushing has suggested, on activation of the anterior lobe of the pituitary body combined with insufficiency of the posterior lobe. The excessive action of the anterior lobe is the condition which, developing later in life, would result in acromegaly, but appearing earlier, as Brissaud suggests, produces gigantism. My patient was certainly of gigantic proportions for his age. Whether further growth would continue cannot be known. I regret that no roentgen ray studies were made of the developmental condition of the bones.

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INTRATHECAL INJECTION OF HORSE SERUM IN THE TREATMENT OF CHOREA

A PRELIMINARY STUDY OF SEVEN TREATED CASES *

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The clinical picture of chorea has never been more succinctly drawn than it was by Sydenham, who first described it as a clinical entity. Little was added to our conception of the disease until the middle of the nineteenth century, when the French clinicians made it a matter of particular study, and later German clinicians and Americans, especially Weir Mitchell and Osler, did much to separate the malady from similar nervous diseases. Later Osler was especially active in attempting to reach the etiology of the disease, together with Stephen MacKenzie he was instrumental in emphasizing the relation of chorea to manifestations of the group of symptoms then known as rheumatism, although as early as 1866 Germain See had insisted on this relationship. MacKenzie was able to relate less than 30 per cent. of his cases of chorea to rheumatism, and later observers, notably Morley Fletcher and Hughes, record similar findings.

With the increasing influence of bacteriology came a suspicion on the part of the medical profession that chorea was an infectious disease. The striking and well authenticated findings of Poynton and Paine, who demonstrated a diplococcus which they claim is etiologic in cases of rheumatic arthritis and endocarditis, and the earlier and somewhat similar findings of Wassermann and Westphal led to a further investigation of the relationship between these two diseases, and the former observers reported the presence of their diplococcus rheumaticus in certain tissues of patients dead of chorea, especially in the spinal fluid, while some of their pupils were able in experimental animals to develop nervous symptoms analogous to the symptoms of chorea as it exists in the human; and from the brains of such animals the *Diplococcus rheumaticus* was recovered. In spite of this work, however, the medical profession for the most part remained unconvinced that chorea is of proved infectious origin, and it must be said that the chemical findings in the spinal fluid and the cell counts, both in this fluid and in the blood, are not what experience would lead one to expect in a disease of bacterial origin.

Pathologists have nevertheless continued their search for an infec-

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tive factor in this disease, but apparently with little satisfaction. The results of bacteriologic examinations have been most contradictory, whether it has been throat secretions, blood or spinal fluid that has been explored. Negative results have rewarded La Fétra, Bartley, Koplik, Morse, Collins and Passini, although streptococci have grown for Richards, Morse and La Fétra in a small proportion of their cases; staphylococci for Donath, diplococci for Apert, Richter and Collins. All these positive results have been reported in cases uncomplicated by symptoms of rheumatism or endocarditis. In instances in which the disease has accompanied rheumatism, tonsillitis or endocarditis, Richards, Poynton and Camesa have reported positive findings of streptococcus or diplo-streptococcus, while Poynton and Paine have recovered the diplo-streptococcus from rheumatic patients and Rothstein a hemolytic streptococcus from tonsils of choreic patients. Spinal fluids in this disease have been cultured by but few, among these Collins, Passini and Morse and Floyd, all of these with negative results. Animal experimentation has been attempted by Poynton and Paine, Pianese, Donath and Dick and Rothstein. None of these observers have reported results that can be considered conclusive. The latest and most suggestive study is that of Quigley.

Quigley reports that of 21 cases studied 10 yielded positive cultures from both the blood and spinal fluid, and 14 in either one or the other. Six bacterial strains isolated from the tonsil, 8 from the spinal fluid and 9 from the blood, were identical in their morphologic and cultural characteristics. It therefore seems to him that bacteria are of importance in the etiology of chorea, and he believes that the coccus described by him is the organism most frequently present in this disease. He finds this opinion supported, not only by his own work, but after a critical review of the work of others. He thinks that the grouping of the organism, its slow, scant, pin-point growth on blood agar, the slight turbidity and the fine granular sediment which it produces in broth, relate it to the streptococci. In the predominance of pairs, with few short chains, and a few irregular groups, when grown in broth, it resembles the streptococci also, and especially the streptococci or diplococci frequently found in rheumatic fever and in endocarditis. It should be noted that the strains studied do not as a rule cause hemolysis on blood agar plates. No definite grouping can be made on the basis of the fermentative reactions as observed.

So far experiments on animals with this coccus, which is being studied further, have been inconclusive.

Although one may not accept the dictum of Faber that "it is generally recognized that chorea is a bacterial disease due to the *Streptococcus viridans* group" it is difficult to escape the conviction that in

many cases, at least, of chorea we are dealing with a general infection with special localization of bacteria or bacterial products in the nervous system. Besides the scanty evidence already quoted, there are a few reports to be found in the literature in which diplococci or streptococci were revealed at necropsy, or in which emboli were found deep in the cortex. However, when one considers that chorea is rarely a fatal disease, necropsy findings on individuals who have died with chorea can not be accepted as conclusively demonstrating the presence of such infective organisms in most cases of chorea. Nevertheless, there is sufficient evidence to justify the physician in an attempt to treat the malady on an assumption of its infectious origin and when the unsatisfactory results that follow the usual methods of treatment are considered, such an attempt seems doubly worth while.

It is the merit of Goodman that he has attempted to apply to the treatment of this disease modern principles of immunity and to introduce immune bodies produced in the patient's blood into the dural space in order that invading organisms shall the more readily be destroyed. His method, briefly, is to remove 45 or 50 c.c. of blood from a vein of the patient, separate the serum and inject this serum into the spinal canal after the withdrawal of a somewhat larger amount of spinal fluid. This injection may be repeated from one to four times. According to his report the results that followed this treatment were amazing. To quote Goodman: "With the autoserum treatment the result is manifest within two or three days—usually one injection is sufficient." Goodman made no differentiation between his mild and severe cases and he classed his results on the basis of the cessation of twitching. In his terminology a "cure" is an absolute disappearance of twitching within a week; "marked improvement," a cessation of twitching within two weeks; "slight improvement" when the movements disappear by the end of the third week; and if after four weeks there is still involuntary movement, he classes the case as "unimproved." Of course, in estimating the cure of chorea much else should be noted besides the twitching. The emotional state of the patient, his fatigueability and the reinstatement of his cerebral inhibition over voluntary movement are of equal if not of greater importance in gaging progress toward returning health.

I was attracted to the Goodman treatment through an opportunity given me by Dr. H. K. Faber to watch the course of events after treatment given one of the patients at the Stanford University Hospital. Faber treated three cases by this method and reported them. He was very much impressed with the results, as in each instance almost complete cessation of the symptoms followed within a week after a single injection of autogenous serum.

In considering the results attained by Goodman's treatment it occurred to me that perhaps the whole effect was attained because the injection of the autogenous serum had set up a sterile meningitis and so had increased the permeability of the choroid to such a degree that antibodies were able to pass from the blood stream into the lymph spaces of the central nervous system. It is well recognized, due to the published work of Mott, Leri, Orofici, Flexner and Mehrtens, supported by other unpublished work, that the injection of foreign protein does break down the defensive power of the choroid and allow substances which ordinarily do not pass to move from the blood into the central nervous system. Goodman, himself, insists that it is necessary to withhold all medication for some days before instituting the treatment. One of his patients who had been receiving chloral and codein, went into deep coma which lasted for thirty-six hours after the first injection. This circumstance was attributed to "some chemical action in the blood plasma which causes a very potent action of drugs when injected into the spinal canal." There is reason to believe, however, that this result was due to an increased choroidal permeability produced by the proteins injected into the spinal canal. This possibility is most clearly set forth in the researches of Flexner and Amoss, who, working on poliomyelitis, first showed that antibodies might be drawn from the blood into the spinal fluid following the introduction of irritants into the subarachnoid space. They were able to grade these irritants in order of their potency from horse serum, which was the most powerful, down to simple drainage of the cerebrospinal canal, which was least irritating. Ranging between these two extremes were the power of heterologous serums, homologous serums, and hypotonic and hypertonic salt solution. Mehrtens has demonstrated that homologous serum injected into the subarachnoid space produces an irritation manifested by a cell count sometimes as high as 1,800 cells to the cubic millimeter, and that a drainage of 30 to 50 c.c. of spinal fluid may be followed by the secretion of a fluid containing as high as 10 to 80 cells. Mehrtens was able to bring sodium iodid out of the blood into the spinal fluid by injecting the drug intravenously six hours after an injection of 10 c.c. of normal horse serum had been made into the subarachnoid space.

These facts, taken together with the knowledge that horse serum injected in the form of immune antimeningococcus serum is innocuous to children, seemed to warrant the use of horse serum by intrathecal injections in the treatment of some cases of chorea admitted to the Hospital for Children in San Francisco. Seven patients have received such injections, and another case has been treated by the method Mehrtens of Stanford University is using in the treatment of cerebrospinal syphilis, namely, the injection of salvarsan six to twelve hours after the

preliminary intrathecal injection of horse serum. Of the cases so treated, one was of the maniacal type, quite the most severe case conceivable; one was of severe hemichorea with pseudoparesis; two very severe; one was of moderate severity, and two were mild, although one of these had been very persistent; three of the attacks were recurrences. The first four patients treated received an initial injection of 20 c.c. of normal inactivated horse serum half an hour after a half c.c. of the same serum had been given subcutaneously in order to test whether or not the patient was hypersensitive to the serum. Five of the patients received a second injection on the fourth, fifth and sixth day following the initial treatment. One little girl reacted so violently to the first injection that repetition was deemed inadvisable, and through a mistake another was allowed to go beyond the period of anaphylactic sensitization, so in this case also it was thought best to forego the second injection. Two patients received injections of 10 c.c. only.

Accepting the premise that the mechanism behind Goodman's results was a protein reaction which let down the choroid plexus barrier that prevents circulating antibodies from entering the spinal fluid, it is obviously of advantage to use normal horse serum instead of autogenous, because the former is more convenient to obtain and to administer and at the same time it is a more potent irritant to the meningeal structures than is homologous serum.

Two sets of unpleasant reactions have followed the use of the horse serum within the spinal canal, an immediate reaction which was evidenced by prostration, by headache, and sometimes by severe vomiting. These phenomena also appear after the injection of homologous serum. They are familiar to those therapists who use the Swift-Ellis technic in the treatment of syphilis. Goodman attributes these untoward symptoms to pressure, but, as in his cases and in this series, uniformly an amount of serum was injected less than that of the spinal fluid withdrawn, pressure cannot be incriminated. The knowledge Flexner and Amoss gained for us about the irritating quality of serum injections is confirmed by the cell counts made by Mehrtens ten hours after the injection of horse serum, when that observer showed a pleocytosis of from 10,000 to 80,000 cells to the cubic millimeter. Further confirmation was had by our own cell counts and the results of chemical reactions in fluids withdrawn from eight to fourteen hours after the injections. It is striking that the only child who showed no improvement after these injections was one whose spinal meninges did not react to the serum by an increased cell count. The second unpleasant reaction appeared after a week and was evidenced by the usual symptom of serum disease; the distressing urticaria was readily counteracted by injections of epinephrin given subcutaneously.

The number of cases treated is too few from which to draw valid conclusions; however, if we use Goodman's criteria, the injections of horse serum have been instrumental in gaining striking and rapid improvement in most cases, but no improvement has been such that a cure can be claimed on the basis of "absolute cessation of all twitching within a week." In fact, only in the mild cases was twitching entirely absent after two weeks, and all three of these patients had been affected for at least three weeks before treatment was inaugurated. One patient, a girl (a mental defective with a neurotic heredity), showed absolutely no reaction to the injections of serum. The most striking results followed the use of the horse serum in the maniacal and very severe cases. Before the serum was used, two of these patients could be kept in bed only by the use of restraining packs, but within forty-eight hours after the first injections both were able to carry a cup to their mouths and to drink without any assistance from the nurse. The restraining pack was no longer necessary and there was a steady diminution in all the excessive movements, while the mental conditions, especially the emotional overflow, were markedly improved. By the end of the third week it was with difficulty that choreic movements could be brought out, but even then they could be elicited by allowing excessive excitement or persistent mental strain to affect the patient.

Undoubtedly the use of horse serum is of great value in controlling these very severe cases. My experience with the Goodman treatment is not sufficient to allow me to express a personal opinion; but, accepting his findings, it seems that the autogenous serum is a therapeutic agent preferable to horse serum in chorea. One would not choose to use horse serum in the treatment of any moderately severe or mild case, but in any attack of great severity the method will certainly bring rapid benefit to the patient.

The last child treated received 5 c.c. of horse serum in the spinal canal, and this was followed in twelve hours by half the normal adult dose of arsphenamin by the vein. The case was an exceedingly severe one, especially on the emotional side, and while there seemed to be marked amelioration, immediately after the treatment, which persisted for some weeks, there has since been retrogression. It is, of course, impossible to draw conclusions from a single case treated so recently, but on the whole the result obtained does not encourage the hope that this is any advance on other methods of treatment.

We have been struck by the fact that injections of smaller amounts of the serum are as effective as are the larger. In future, in applying this technic, not more than 5 or 10 c.c. of serum will be used at a single injection. The value of repeated injections also seems to be demonstrated. The headache and depression that followed the first injection are rarely manifest after subsequent treatments.

The fact that the withdrawal of blood from a donor and the preparation of a sterile homologous serum present great technical difficulties, while sterile normal horse serum is easily obtainable and the technic of its use is simple, led to the hope that the use of the latter agent might give the profession a valuable means of dealing with a distressing malady. A measure that could be applied without harm to patients outside the protecting walls of a hospital. The cases here reported are too few to say that the hope is realized, but there can be no doubt that in the most severe cases the injections of normal horse serum bring about rapid diminution of the more explosive symptoms. Parents who naturally are uneasy during the stage of first reaction following a treatment are uniformly delighted at the promptness with which their children gain control of movement and speech and lose their emotional excitability.

Of course, this method is no panacea for chorea. The fact that these children have a congenital inferiority of the nervous system means that rest and overfeeding will always be essential parts of the treatment. Head's dictum that the cure for chorea is six weeks in bed, four eggs and two quarts of milk a day, must still be remembered; nor must it be forgotten that any focus of infection, especially if it be in the tonsil, must be removed. Warm baths and massage ought never be omitted from the regimen. Care must also be taken to heed the psychologic reaction inevitable between choreic patients and their environment. Therefore, it is wise to keep the family and the usual attendants away from close contact with such children during the course of treatment. Under such management mild cases of chorea will rapidly achieve normality. However, when the patient is affected with severer forms the results of such measures are delayed for weeks or months. In these circumstances the little patients become a great distress to themselves and to all about them, and it is to such that the intrathecal injections of horse serum offer a therapeutic aid which is harmless and which at the same time will bring prompt relief to the more dominant symptoms, and probably, though not certainly, will hasten the final recovery.

While there is no certainty that chorea is an infectious disease, treatment based on that idea can be warranted only by clinical results. Never can the psychic disturbance of chorea be overlooked, and it may well be that the results which follow the use of serums are evidence of a successful, if unwitting, application of suggestive therapy. At any rate we have every right to hope that further investigation will establish the serums as valuable measures in the treatment of selected cases of chorea.

SUMMARY OF CASES

CASE 1.—O. W., boy, aged 11 years; second attack; duration two weeks from commencement of treatment; very severe maniacal delusions and great excitability; had to be restrained in bed; characteristic twitchings; unable to speak intelligibly; heart normal; tonsils showed chronic infection. Injection of 20 c.c. of serum given, followed by vomiting, prostration, slight pyrexia, and immediate exaggeration of all symptoms; reaction disappeared in thirty-six hours. Second injection of 20 c.c. was given on the fifth day following. All twitching had disappeared in forty-eight hours. The excitability with emotional overflow persisted for about two weeks. Besides the serum treatment, the patient had continuous hot packs, a high calory diet, and during the third week in the hospital, tonsillectomy. There was a relapse during the two weeks following the removal of the tonsils. During the next two weeks all symptoms disappeared. The patient was dismissed and has remained free for two months.

CASE 2.—M. P., girl, aged 8 years. The patient, who had a neurotic family history and was a masturbator and a mental defective, had had a persistent chorea with short periods of remission for the previous three years, although the manifestations were mild. Her symptoms were twitching, emotional excitability and overflow, a clumsy gait and blurred speech. Her heart was normal; throat was healthy. She was given 20 c.c. of serum on two occasions, four days apart. A slight reaction, with vomiting, headache and low fever, persisted for forty-eight hours after the first injection. She had slight diminution of symptoms after the second day, but final result showed her to be no better than before treatment. This is the only case in which some definite influence over the course of the disease was not manifest.

CASE 3.—J. H., girl, aged 11 years; second attack; was very severe. There were many other cases of chorea recorded in the family history. She had been ill for eight weeks. Her symptoms were twitching, persistent headache, speech disturbance, excitability, emotional overflow. She had chronic inflamed tonsils and had suffered from recurrent tonsillitis. She received 20 c.c. of serum without a second injection and she reacted to the serum with headaches, stiff neck, stiff legs, vomiting and later a severe urticaria, all of which symptoms disappeared within forty-eight hours. Improvement began at this time and continued uninterruptedly. She was dismissed after three weeks perfectly well. Besides the serum she received a high calory diet and a short course of hot packs.

CASE 4.—L. S., boy, aged 13 years; severe attack, hemichorea type, which was the second attack. He had suffered from a very severe seizure two years before. The duration of the present attack was three weeks. Symptoms were twitching, right pseudoparesis, emotional disturbance, speech disability. He was hardly able to walk. The heart showed a slight systolic blow; no endocarditis. He had chronic recurrent tonsillitis. Received 10 c.c. of serum and no second injection. He reacted with headache, slight urticaria and slight purpura, all of which disappeared in thirty-six hours. He showed a steady improvement and had a slight relapse lasting for about three days after the removal of his tonsils during the second week of treatment. He was dismissed in a month, having showed no further symptoms after the third week. There had been no return of symptoms up to the fourth month.

CASE 5.—D. J., girl, aged 13 years. This was a very severe attack, with frequent exacerbations. The patient was so uncontrolled that she had to be restrained in bed. This was the first actual attack, although she had been "very nervous" for the past five months. The actual attack was of three weeks' duration. The symptoms were twitching, loss of motive power, loss of intelligible speech, emotional overflow and a mild adiadokokinesis. Her heart was normal. Her tonsils were slightly injected. She was given an initial dose of 20 c.c. serum and five days later another 20 c.c. She had a violent reaction to the first injection with extreme vomiting and some pyrexia, which persisted

for thirty-six hours. A week later there was marked urticaria for one day which was well controlled by epinephrin subcutaneously. The alleviation in this case was striking. The child, who was utterly helpless before treatment, was able within forty-eight hours to feed herself and to drink water from a cup unaided. She went on to complete recovery and was dismissed without symptoms at the end of her third week in the hospital. She was given high calory diet, hot packs, as well as serum treatment. A cure could not be claimed, because she was still highly emotional, and she had a short relapse two months after leaving the hospital.

CASE 6.—V. B., girl, aged 10 years. First attack, but "always nervous." The duration of the attack was three weeks. It was a mild case, evidenced by twitching, emotional overflow and slight speech disturbance. Her heart was normal. She had chronic recurrent tonsillitis. The first injection was 7 c.c. of serum and the second 10 c.c. The reaction was slight and she complained of a mild headache and backache. She had low fever and was restless. The symptoms of chorea were exaggerated for the first two days; then there was steady improvement. Her tonsils were removed two days before the serum was injected. She was given high calory diet. Her progress was uninterrupted and the symptoms had disappeared entirely in three weeks.

CASE 7.—R. M., boy aged 14 years. Family history not neurotic. This was the fourth attack. The boy had suffered from an attack of rheumatism in his eighth year, and this was followed by chronic endocarditis, and a pseudoparetic chorea, lasting four months. There was a third attack following this, which lasted for six weeks. There was a second attack which lasted six months. His tonsils had been removed between the second and the third attacks. The present seizure had lasted two weeks. He had lost power to use his right hand, he dragged his right leg, his speech was greatly disturbed, he had marked choreic movements and emotional overflow. His heart showed the evidence of old endocarditis; his throat was healthy, tonsils out. He received an initial injection of 20 c.c. of serum and a second dose four days later of another 20 c.c. After the first injection he reacted with headache, vomiting, anorexia and the choreic symptoms were worse. Within forty-eight hours this reaction abated and from that time he made a rapid improvement. Packs and high calory diet were also prescribed. The symptoms were entirely gone in two weeks and he had no return after six months.

BREATH HOLDING IN INFANTS*

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Breath holding (also known as hysterical laryngospasm, rage spasm, and inspiratory apnea) is a condition not infrequently observed in early childhood. At first glance one would be led to believe that the attacks are manifestations of spasmophilia or tetany with the associated laryngismus stridulus, but on closer investigation it will be discovered that such assumptions are erroneous. The breath holding attacks, as distinguished from laryngismus stridulus, manifest no true laryngeal spasm. The breathing stops suddenly in the midst of a crying attack, but there is no inspiratory spasm.

The attack may be briefly described as follows: The child works himself into a rage, cries for a time, and then suddenly stops, finding it impossible, for a brief period, to make any further sound. The inspiratory muscles remain in a tonic state. The child throws himself about and becomes cyanotic or pale. Then the body becomes rigid and the eyes turn or become set. For a moment it seems that the child is asphyxiated. The attack usually lasts a few seconds and then disappears. It may, however, continue for several minutes, while in the more severe cases it may be followed by convulsions.

Barthez and Rilliet are among the first to speak of breath holding. They describe it as a condition occurring in passionate (angered) children, manifested by a suspension of the respiration accompanied by suffocating inspiration, during which the face becomes purplish and the extremeties cold. Sometimes it is followed by an eclamptic attack. They say it is not possible to distinguish breath holding from glottis spasm.

Ibrahim reports three cases, the first two of which are dismissed with only a short reference. In the first there had been laryngismus stridulus of the ordinary type in early infancy. In both, the rage spasms were characterized by emotional excitation, cyanosis, unconsciousness, and great drowsiness. The third case is described in great detail, the principal points of which were the following: The mother was an extremely nervous woman and is said herself to have suffered from rage spasm during infancy. The infant thus had a nervous stigma, although there was neither epilepsy, insanity, nor other ner-

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vous disease in the family history. Ibrahim had this baby under observation since earliest infancy. During the second year, the child in the midst of a crying attack would hold its breath and become cyanotic; the body would grow limp. Respiration would apparently cease. At the end of the attack, the child would cry lustily for a few moments and soon afterward fall asleep.

Ibrahim calls attention to the fact that all the classical signs of tetany, including the electrical reactions, were searched for but were not found.

H. Neumann[1] in his discussion of breath holding, tries to differentiate it from tetany. Laryngismus stridulus, he says, is a manifestation of spasmophilic diathesis or tetany and tends to disappear during the first year or two of life; whereas the inspiratory apnea or breath holding attack is an early symptom of neurasthenia. He also says that in numerous cases which he has examined, the classical signs of tetany were usually absent. There was one exception, however, a boy of 4 years, who, suffering evidently from rage spasm, showed very definitely Chvostek's facial phenomenon. His father, who was an extremely neuropathic individual, showed the same sign.

A further differentiation may be made in addition to Neumann's observations. Attacks of breath holding occur commonly in the second and third years of life and tend to disappear about the fifth; whereas genuine spasmophilia makes its appearance during the first year or two.

It will occur to everyone that the resemblance between these breath holding attacks and minor epilepsy is such that the differentiation of the two may at times present great difficulties. It should be remembered, however, that breath holding attacks follow immediately after severe crying, excitement, or anger; while epileptic attacks occur suddenly in the midst of quiet play or even during sleep. Biting of the tongue, which is characteristic of epilepsy, does not occur in breath holding. On the other hand, involuntary evacuation of the bladder or rectum may occur in either attack. Another point of resemblance is the prolonged sleep usually following an attack which is characteristic of both conditions.

Neumann reports a case in which breath holding attacks or rage spasm occurred in an epileptic child 3 years old. He had suffered from epilepsy since his third month of life and presented at times unmistakable convulsive seizures. On certain occasions, however, when he lost his temper or became frightened, he would hold his breath, become cyanotic, and after a brief period would lapse into a deep sleep.

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[1] Arch. f. Kinderh., **42.**

It would seem that an important point in the differentiation of the two conditions is to be noted in each case in the progress of the disease, namely, that breath holding attacks tend to recover completely, while epilepsy, as a rule, persists.

I have seen on several occasions attacks of whooping cough in young infants and children that required differentiation from breath holding seizures. A few days ago, for instance, a child was brought into my office because of peculiar respiratory attacks that alternated with coughing. At night the child not infrequently had severe coughing attacks which the parents thought resembled whooping cough. During the day, however, the coughing was substituted by paroxysms of breath holding; undoubtedly they were voluntary attempts to suppress the cough. They were characterized by extreme cyanosis, great prostration, relaxation of muscles and momentary unconsciousness. The baby gives one or two short coughs, then she becomes blue and rigid. She has a facial spasm, the eyes become set and roll upward, arms and legs are rigid and the mouth is tightly closed. The attack lasts several minutes. Cyanosis disappears, normal breathing is resumed and consciousness returns. This seventeen months old baby had such an attack in my office. These alternating attacks of coughing and breath holding had been going on for four or five weeks, during which time one or more typical whooping cough paroxysms occurred almost nightly.

I also recall the history of a baby 2 weeks old who acquired whooping cough from the mother. The child began to cough when it was only 10 days old. Each paroxysm was characterized by a slight crowing. He would become intensely cyanotic and fall limp in the mother's arms with complete respiratory cessation. At such times, the pulse was slow and the child seemed lifeless. After a few moments the patient regained color, and breathing proceeded normally. The baby ultimately recovered.

Cases of breath holding are not of uncommon occurrence. Very often they are the cause for emergency calls for the medical attendant, though as a rule, he discovers when he arrives on the scene that the child has recovered. Only the other day a mother came to my dispensary clinic with a large, well developed baby of 22 months, who presented all the characteristics of breath holding or rage spasm. The mother described in minutest detail all of the points which have already been referred to. If the child was crossed or thwarted in any way, it would cry, hold its breath, become cyanosed and momentarily unconscious. The child was very well nourished, presented no evidence of rickets, no carpopedal spasm, and no Chvostek or Trousseau signs.

Another case further illustrates the disorder. A mother brought

her 17 months old baby to us on May 5, 1918, because of anemia and great fretfulness. The child had always been delicate and sickly, was very difficult to feed, and suffered from severe malnutrition. She was extremely irritable and cried much of the time. About two weeks before we saw her the child began to fret more than usual, would become extremely irritable and work herself into a rage, which would be followed by a breath holding spasm. The mother said that five or six of these attacks occurred daily. None of the typical signs of tetany was present, though there was a slight increase of electrical excitability. We improved the child's feeding and suggested a plan of psychotherapeutic treatment which the mother, who was a very intelligent woman, immediately adopted. She refused to pick up the child when she cried, treated her sternly, shook her finger at her, and reproved her when a breath holding attack was imminent or in progress. The treatment finally proved successful. Although on the first day after the baby's admission to the hospital we were enabled to witness several typical attacks which consisted of fits of temper, crying, breath holding, cyanosis and momentary unconsciousness, on the second day they had completely ceased.

These attacks of breath holding occur in neuropathic children and are brought on by fear, anger, fright, or some other psychic trauma. As a rule, children subject to such seizures are irritable and ill-tempered. The condition is very often aggravated by neuropathic parents who, fearing the recurrences of these attacks, humor them in every possible way, permitting no one to cross the child and allowing no whim or caprice to remain ungratified. It is obvious, of course, that such treatment does not help the child to build up any degree of resistance to the recurring attacks.

After some time has elapsed, most of these patients practically recover, although in some instances, as has been pointed out, the attacks may be severe and protracted. Children who fall ill with an acute infectious disease, or who, by reason of accident or injury, require surgical treatment, may be seized with a severe breath holding attack, accompanied by general convulsions, as a result of the fright which they have sustained. Under such circumstances the attack may be so severe as to terminate fatally.

Treatment should be directed toward the general management of the nervous child. Mental stimulation of every kind should be avoided. He should be ignored as much as possible by parents and friends. When the attacks occur, there should be no fussiness or consternation, or any of the hysterical manifestations usually evinced by mother or nurse. Cold water dashed into the face has been suggested as a direct

remedy. Finally, the patient should be shown in no uncertain manner that any repetition of the attack will meet with harsh if not painful measures.

Frequently the patients improve most rapidly when they are removed from the excitement and tension of home surroundings. A short stay at the hospital away from parents and friends is often advisable. At times a short course of bromids may be required in addition to psychotherapy.

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BALANTIDIUM COLI INFECTION WITH REPORT OF A CASE IN A CHILD*

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There appeared in my service in the outpatient department of the Touro Infirmary in New Orleans an interesting and unusual case of dysentery which because of the age of the patient, the source of the infection and the character of the organism found deserves recording if for no other reason than as a reminder of another possible etiologic factor in the production of frequent stools. The infrequency of many diseases in childhood undoubtedly is in great part due to lessened exposure incident to age. This explanation advanced several years ago in the instance of amebiasis in children may also be suggested for the rare infection in childhood of this unusual offender in man.

While the case was not observed for as long a time as would have been preferred, nevertheless for the foregoing reasons and because of the easy means of its recognition, this case of *Balantidium coli* in a child is reported.

REPORT OF CASE

History.—A colored boy 5 years of age was brought to the outpatient children's department at Touro Infirmary by his mother who stated that the child had been having a diarrhea for nearly a year, but that recently she noticed blood in his bowel movements. During the period from the first attack of diarrhea to the present time there had been intervals when the child was apparently well and had no bowel trouble. With this last attack, however, blood had appeared and he seemed sicker than ever. The attacks were progressive in severity, each one being worse than the one preceding. He strained when his bowels moved, complained of pain in his stomach, had no appetite, and had been losing weight. He had been accustomed to help "round up" the pigs in the pen every day and frequently would eat some food which he would hold in his hand while helping with the pigs. It was his habit also to go into the pen at times when he ate his food.

The family history was negative, except that the father, who tended the pigs, had a diarrhea a short time previously, the character of which could not be ascertained.

Past History.—The patient was a full term child. He had never been ill before the diarrhea, and had always been nourished as other children of his race.

Physical Examination.—This showed a patient poorly nourished but fairly well developed. His skin was dry, as was his tongue and mouth. There was a catarrhal stomatitis. His eyes were sunken. His lungs, heart, liver, spleen and abdomen were negative except for some tenderness over the lower abdomen. The nervous system was also negative.

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A rectal tube was passed and some bloody mucus obtained, which was immediately examined and revealed the presence of *Balantidium coli.*

As there were no beds available at Touro Infirmary he was referred to my service at the Charity Hospital, but unfortunately he never appeared at the hospital and was lost sight of.

Description of Organism.—The organisms seen in this case belonged to the infusoria variety of the protozoa and are known as *Balantidium coli.* They were oval-shaped, more pointed and tapering at one end and rounded at the other, and measured from 0.07 to 0.1 mm. in length by 0.05 to 0.07 mm. in breadth. The mouth was funnel-shaped and situated on the ventral side of the organism a little below the anterior or pointed pole. A thick layer of long cilia was found around the peristome, which continued actively a circulatory motion, and by the use of which the organism grasped its food: various cells, bacteria, and blood cells. The funnel-shaped mouth extended backward and downward and communicated with the endosarc.

The endosarc consisted of granular matter both fine and coarse and highly refractile, inclosed in a thin and very transparent sheath, which was a continuation of the gullet above and which ended at the anus situated at the posterior or more rounded pole. A kidney-shaped nucleus, which changed its position with the motion of the granular matter, was found in the endosarc usually below and to one side of the peristome. Vacuoles were seen in the endosarc numbering from one to six, usually two, and were apparently contractile. These vacuoles according to Stein[1] are connected by lacunae, which probably explains the large single vacuole sometimes seen which occupies the whole lower third of the parasite.

A thick cuticle longitudinally striated inclosed the endosarc and was separated from it by a narrow rim of homogeneous protoplasm (the ectosarc). These striations, undoubtedly muscular structures, extended from the peristome on the ventral surface and from a corresponding level on the dorsal surface to the anus of the posterior pole.

Cilia extending throughout the entire length of these striations controlled the movements of the parasite.

By means of these cilia and muscular bands the parasite was able to move with tremendous rapidity and comparative ease through fields containing large particles of matter. The parasite was capable of changing its shape and direction with great facility by contracting the muscular bands.

At times the organisms appeared quite round.

Encysted forms of the parasite have been described by Leuckart[2] and Stein,[1] in which the organism becomes rounded, loses its cilia, the endosarc contracts and contains fat globules, the nucleus becomes obscured, and it is surrounded by a thick capsule.

From the careful observations of Bel and Couret[3] through the entire cycle the method of reproduction of these infusoria is by budding conjugation and binary fission. Many other methods of conjugation and reproduction have been described by Wising,[4] Woit,[5]

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1. Stein, F.: Bohmisch. Genzell der Wissenchaften, 1860, p. 165; Amtl. Ber. d. Karlsbad, Naturforch., 1862.
2. Leuckart: Die menschlichen Parasiten, 1863, p. 1; Parasiten des Menschen, 1879, p. 3.
3. Bel and Couret: Balantidium Coli Infection in Man, Jour. Infect. Dis., 1910, **7,** 609.
4. Wising, P. J.: Nord. med. Arch., 1871, **3,** No. 3, Stockholm; Ibid., Svensk. Läk. Sällsk. Handl., 1885, p. 48, Stockholm.
5. Woit, O.: Deutsch. Arch. f. klin. Med., 1897, **60,** 363.

Gurvich,[6] Bushuyeff,[7] Lavrovskaya,[8] Zhegaloff[9] and Daflein.[10] The observations of Bel and Couret[3] with regard to reproduction conform to those of Ekecrantz,[11] Wising,[4] Leuckart,[2] Strong[12] and others.

Conflicting results have been obtained from animal experimentation by Wising,[4] Lavrovskaya,[8] Strong,[12] Zhegaloff,[9] Rapchevski,[13] Chigayeff,[14] Vlayeff,[15] Cassagrandi and Barbagello[16] and Chichulin[17] by injecting feces containing balantidia in cats, dogs, rabbits, pigs and monkeys.

Grassi and Calandruccio[18] produced no results on themselves after injecting balantidia from the hog.

Leuckart[19] describes these organisms as being much less sensible to the influence of water and cold than other nomads, and as preserving their viability and motility for long periods in water at ordinary temperature. Klein[20] recognized an organism which he believed to be *Balantidium coli* which he secured from sewage and which after being bottled in sewage lived and were yet motile in thirteen weeks. On the other hand, Malmsten[21] concluded that the parasite is short lived, since it died shortly after removal from the intestine, and Zhegaloff[9] was of the same opinion. From the various statements made by observers it may be said that the length of time the organism may live is variable. Attempts to prolong their lives in feces by Bel and Couret[3] were unsuccessful at various temperatures, as were also their attempts at the cultivation of the organism. Other observers have met with the same negative results, and Strong[12] states that the parasite has not been grown or isolated in pure cultures.

Balantidium coli were probably first observed by Lieuwenholk[22]

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6. Gurvich, M. J.: Russk. Arch. Patol., I. Bakteriol., 1896, **2,** 804.
7. Bushuyeff, V. F.: Voyenno-medic. Jour., 1897, p. 188, Med. Spec. Part, p. 167.
8. Lavrovskaya, Y.: Bolnitch Gaz. Botkina, 1891, No. 11, p. 304, St. Petersburg.
9. Zhegaloff, J. P.: Klin. Jour. Mosk., 1899, **1,** 44.
10. Doflein, F.: Die Protozen als Parasit. u. Krankheitserreger, Jena, 1901.
11. Ekecrantz, W.: Nord. Med. Arch., 1869, p. 1, Stockholm.
12. Strong, R. P.: Dept. of Interior, Bureau of Govt. Lab. Biol. Survey, No. 26, December, 1904.
13. Rapchevski, I. F.: Vratch, St. Petersburg, 1880, p. 505; Med. Vestulk, St. Petersburg, 1882, **21,** 361, 377 and 393.
14. Chigayeff, N. F.: Vratch, St. Petersburg, 1898, **19,** 1441.
15. Vlayeff: Vratch, St. Petersburg, 1898, **19,** 140.
16. Cassagrandi and Barbagello (Quoted by Strong, Footnote 12).
17. Chichulin, G. N.: Voyenno Med., 1900, **78,** Med. Spec. Part, p. 3059, St. Petersburg.
18. Grassi and Calandruccio: Acc. d. R. Acad. d. Linc., Roma, 1888, 285, series 4, vol. 4, p. 700.
19. Leuckart: Brit. Med. Jour., Dec. 19, 1896, p. 1797.
20. Klein, E.: Brit. Med. Jour., 1896, **2,** p. 1852.
21. Malmsten, P. H.: Allg. med. Centr. Ztg., Berl., 1858, **27,** 81.
22. Lieuwenholk: Quoted by Strong, Bull. Johns Hopkins Hosp., 1901, **12,** 31.

in his own stools in 1857. In 1857 Malmsten and Loven[23] first described them as *Paramecium coli,* and five years later (1862) Malmsten[24] reported two cases. Stein,[1] in 1862, proposed the name of *Balantidium coli.*

In 1891 Mitter[25] was able to collect only twenty-eight cases. Strong,[12] in 1901, only 117 cases, including reports from Africa, Cochin China, Cuba, Finland, Germany, Italy, North and South America, Philippines, Russia, Sunda Islands and Sweden.

In the United States probably the first case to be reported was in Iowa by Mitter[25] in 1891. Since then cases have been reported by Bel and Couret,[3] 1 in Louisiana; Gray,[26] 3 in Arkansas; Deaderick,[27] 1 in Eastern Arkansas; Sistrunk,[28] 1 in Minnesota; Rockefeller Sanitary Commission,[29] 2 in North Carolina and 1 in Mississippi; Jennings,[30] 1 in New York; Bowman,[31] 2 in the Philippine Islands; and Young and Walker,[32] 1 case in Oklahoma.

In all, the literature contains considerably less than 150 reported cases of this infection in man. Men have been infected twice as frequently as women, and in the cases reported all have been adults with the exception of two cases in children.

The habitat of this infusorium in the human being is in the large intestine, but they have been found in the appendix (Malmsten[21]).

Leuckart[33] was the first to show the pig to be the normal host of the *Balantidium coli.* He suggested that the possible way infection occurred was by the entrance of the freshly voided parasites into the alimentary tract of the human being. He also suggested ingestion of the organism in the encysted state as a probable method of infection.

Deaderick[27] says that besides the domestic pig, certain species of monkeys serve as hosts for the balantidium.

The observation of Klein,[20] who found an organism he believed to be the *Balantidium coli* in the sewage of London, and also in the

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23. Malmsten, P. H., and Loven: Infusurier säsom intestinaljar homemeskan, Hygeia, Stockholm, 1857, **19,** 491; Virchows Arch. f. path. Anat., 1857, **12,** 302.
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25. Mitter, J. J.: Beitrag z. Kenntness zur Balantidium Coli in Menschlichen Darmkanale, Kiel, 1891.
26. Gray, D. A.: St. Louis Med. Rev., April 27, 1907.
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31. Bowman, F. S.: Studies in Balantidium Infection, Med. Rec., New York, April 22, 1911.
32. Young, A. O., and Walker, O. J.: Balantidium Coli Infection in Oklahoma, Jour. Am. Med. Assn., 1918, **70,** 507.
33. Leuckart: Weighman's Arch., 1861, **1,** 80, Plate V, Fig. A, B; Die menschlichen Parasiten, 1863, p. 146; Fig. 21, p. 744.

drinking water of the same city as delivered to the consumer, suggests the entrance of the organism through drinking water as a means of infection.

It is of interest to note that in about 25 per cent. of the cases reported infected with *Balantidium coli* there has been either direct contact with swine or the infection has followed ingestion of food products from pork.

An entire family infected with *Balantidium coli* after eating sausages made from a hog which had harbored the organism is reported by Chichulin.[34]

Henschen[35] especially emphasizes the pathologic importance of the parasite, while other authors are inclined to believe the presence of the parasite to be an accidental or unimportant complication.

In 1900 Opie,[36] in his article on protozoa, concludes "that *Balantidium coli* is apparently an accidental parasite which finds favorable conditions for growth in the diseased intestine, and that it is improbable that the organism is the etiologic factor in the production of the diarrhea with which it is associated."

McFarland[37] holds that the organism is not certainly parasitic, but perhaps merely commensal; that is, it inhabits the body of its host, but without any effect on the host either detrimental or advantageous.

Malmsten[21] and Doflein[10] believe the organism to be harmless, but Strong,[12] Brooks,[38] Solowjew,[39] Bel and Couret[3] and others believe the balantidium is an important etiologic factor in the production of the catarrhal and ulcerative lesions of the large intestine in the infection associated with its presence.

Certainly the cases of Strong and Musgrave[40] and Bel and Couret,[3] which have been so carefully and minutely studied, are conclusive evidence of the pathogenicity of the organism. To quote their conclusions:

Strong and Musgrave:[40] We cannot regard this parasite as a harmless one for we could not explain the persistent diarrhea of our patient without regarding it as the exciting cause, nor were we from the lesions found at necropsy enabled to explain his death in any other way.

Bel and Couret:[3] Finally, from the definite and constant microscopic findings and negative blood and cultural results for other intestinal invaders, the logical conclusion seems to be that *Balantidium coli* is not a harmless commensal, as some suppose, but an organism able to invade the human tissues and cause a serious disease; death may follow through compression of the intestinal glands by a hyperplasia of interglandular tissue produced by the parasites and through glandular necrosis and absorption of toxins from any terminal bacterial invasion.

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34. Chichulin, G. N.: Loc. cit., Footnote 17.
35. Henschen: Quoted by Strong and Musgrave, Footnote 42.
36. Opie: Twentieth Century Practice of Medicine, 1900, **19.**
37. McFarland: Quoted by Jennings, Footnote 30.
38. Brooks, H.: New York Univ. Bull. Med. Sc., January, 1902.
39. Solowjew, N.: Centralbl. f. Bact., Ref., 1901, **29,** 821 and 849.
40. Strong and Musgrave: Bull. Johns Hopkins Hosp., 1901, **12.** 32.

The infectious character of the *Balantidium coli* is seen in the observations of Brooks[40] on a fatal dysentery among the apes in the New York Zoological Garden, and the pathology of the infection in man is clearly shown by the necropsies and studies of Strong and Musgrave,[42] Solowjew,[41] and Bel and Couret.[3]

The organisms invade all the coats and blood vessels and lymph channels of the large intestine and the neighboring lymph glands, and produce a hyperplasia and cell infiltration either mechanically or through the liberation of cytolytic ferments. Ulcers which are small and shallow and mostly limited to the mucosa are found which are probably due to the terminal invading bacteria, the balantidium coli primarily producing avenues of entrance, as they are absent from the walls of the ulcers; some, however, penetrate the muscularis mucosa. The organisms produce a subacute or chronic inflammation of the interglandular tissues and submucosa.

The presence of the organisms in the blood vessels and lymph channels argues for the possibility of carrying infection to the liver and lung through these routes (Couret and Bel[3]).

The patients suffering with this infection may have digestive troubles, but usually have a diarrhea or dysentery. The stools are liquid and may contain undigested food. There is usually mucus or blood, the stools resembling those seen in amebic dysentery. These may be from a few to many in the course of the twenty-four hours. Tormina and tenesmus are frequent, the latter particularly if the lesions are situated near the anus.

The symptoms may subside for a period, to begin again. In those cases of prolonged duration anemia may be found and there is great loss of weight. At times there is edema. In some cases severe and pernicious anemia has been suspected. The course of the disease is usually progressive.

Examination of the blood usually shows slight variations from the normal and there may or may not be an eosinophilia.

The skin is dry, the temperature is normal or there may be a rise up to 99 F. Hebetude is present to a greater or lesser degree, the tongue is dry, at times a stomatitis may be present. The lymph nodes are occasionally enlarged. Emaciation is a common symptom.

The urine shows nothing of interest.

Proctoscopic examination usually reveals the rectum and lower colon lined with thick, bloody mucus covering the shallow ulcers which readily bleed.

The diagnosis is promptly made by the examination of the stools or by introducing the rectal tube and examining some of the bloody stained mucus, when the characteristic organisms are easily discern-

able. By examining the fresh specimen while it is still warm the parasite is found to be very active, but it becomes more sluggish as its surroundings become colder.

The duration of the diarrhea in patients known to be infected with the parasites has been as long as fifteen years.

All the reported cases, with two exceptions besides this one, have been in adults. The age of this patient is next to the youngest recorded, the other two being 4 years and 5⅓ years, respectively.

The prognosis depends on the ability to rid the host of the balantidia. Many cases are shown wherein the relative decrease in the numbers of the parasites is coincident with a corresponding improvement of the patient.

Remembering the pathology of the disease, with its possible complications in the liver and lungs, it may be said that the earlier the diagnosis and the more thorough the treatment the better the prognosis. The mortality has been given as high as 30 per cent. by Strong.

From the information available the prophylaxis should be directed toward the care and hygiene of those who are in close contact with the care of swine and the manufacture of pork products, and the thorough cooking of the pork products before ingestion. If to this is added a safe water supply, prophylactic measures against this infection will be as complete as our present knowledge will warrant.

Many drugs have been employed in the treatment of this infection, mostly by colonic flushing and by enema. Quinin, tannic acid, silver nitrate, iodin, acetic acid, salicylic acid and boric acid, methylene blue, thymol in olive oil followed by castor oil, have all been employed. By mouth arsenic and thymol have been used.

There is as yet no known specific in the treatment of this disease, but because of the resemblance of this infection to that of amebic dysentery: (1) in the invasion and location of the organisms in the tissues; (2) in the histologic pathology; and (3) in its clinical manifestations, it would seem that ipecac or its alkaloid, emetin, should be employed, as it is hardly to be expected that local flushings will be of any avail after the infection is established.

If in reporting this case I may only have stimulated interest as to the possibility of this parasite being a cause of frequent stools and placed the physician on guard for the recognition of this infection, which has been shown to exist not only in tropical and subtropical climates, but in the colder climates as well, where the symptoms are less severe, I will feel that the purpose of this paper will have been subserved.

NOTE.—Since writing this paper another case has come to my knowledge in which emetin was employed in its treatment, and, I am told, with spectacular results.

PROGRESS IN PEDIATRICS

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